UNITED STATES DISTRICT COURT
FOR THE
DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY, and MANULIFE INSURANCE COMPANY (f/k/a INVESTORS PARTNER LIFE INSURANCE COMPANY),	)	CIVIL ACTION NO. 05-11150-DPW
Plaintiffs,	)	
v.	)	
ABBOTT LABORATORIES,	)	
Defendant.	)	

AFFIDAVIT OF STEPHEN J. BLEWITT

CONTINUATION OF EXHIBITS

PLs' I

February 2001 — ABT-518

Feb-01 — **ABT-518 Matrix Metalloproteinase Inhibitor**

Franchise	Dev. Status	Brand Name	Generic Name	Patent Exp.	Indication(s)
Oncology	Phase I	TBD	TBD	2018	Solid tumors such as breast, non-small cell lung, ovarian and colorectal cancers; non-Hodgkin's lymphoma

Description

ABT-518 is a metalloproteinase inhibitor that selectively targets MMP-2 and MMP-9, metalloproteinases that have been implicated in the progression of cancer

In preclinical studies ABT-518 inhibits tumor growth in a variety of murine tumor models when administered alone, or acts synergistically with cytotoxic agents ABT-518 also blocks blood vessel formation in a murine angiogenesis model

	Unit	Value	CAGR	Unmet Need/Key Market Drivers	Key Competitive Positioning/Market
U.S. Market	TRX	NA		Despite major advances in our understanding of the molecular events that underlie cancer, this disease remains the second leading cause of death in the US, with more than 550,000 cancer deaths last year alone Today advanced cancer is primarily treated with a combination of cytotoxic agents that typically offer limited efficacy coupled with debilitating side effects New therapies that demonstrate a clinically significant improvement in efficacy (survival or time to disease progression as a surrogate to survival) and limited side effects have significant market opportunities	MMPIs (e g, BMS-275291, prinomastat), Taxanes, Taxol, Taxotere and generic paclitaxel, Other cytotoxics such as Gemzar, Navelbine, Camptosar, Xeloda, Platinol and Paraplatin Antibody therapies such as Herceptin and Rituxan; Emerging cytostatic agents such as tyrosine kinase inhibitors (e.g. Iressa, SU5416), FTIs, and other angiogenesis inhibitors (e.g. endostatin, angiostatin) The competitors will vary depending upon the cancer type(s) where ABT-518 demonstrates efficacy
	Sales	$3,500 MM	14% global		
Ex-U.S. Market	TRX	NA		There are significant unmet needs in cancer Ex-US, where cancer is the leading cause of death in Japan and the second leading cause of death in Europe Physicians are looking agents that demonstrate improved efficacy when used either as single agents or in combination with existing regimens	Competitors are similar to those in the US. Government agency analysis for cost effectiveness of the therapy is important for reimbursement in some countries.
	Sales	$4,700 MM	14% global		

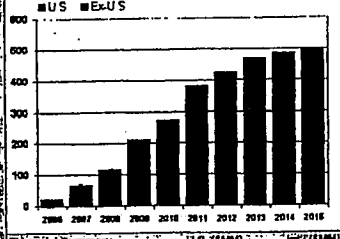
Development

Cost to NDA	DDC Est.	Thru 2000	2001 YTD	2001 Proj.	2001 Budget	2001 Var.	2002	2003	2004	2005	Post LRP	Total
Clinicals	$0 0	$1 6	$0 3	$2 2	$2 2	$0 0	$19 0	$21 0	$19 0	$16 0	TBD	$76 8
CMC	$0 0	$1 9	$0 1	$2 2	$2 2	$0 0	$8 0	$5 0	$4 0	$4 0	TBD	$25 0
Drug Safety	$0 0	$1 8	$0 6	$2 3	$2 3	$0 0	$8 0	$4 0	$3 0	$2 0	TBD	$21 1
Other	$0 0	$0 4	$0 1	$0 7	$0 7	$0 0	$3 0	$5 0	$3 0	$1 0	TBD	$13 1
TOTAL	$0 0	$5 5	$1 1	$7 4	$7 4	$0 0	$38 0	$35 0	$29 0	$23 0	TBD	$139 0

	DDC ($MM)	LBE	Actual
Start of Tox			2Q2000
Phase I		1Q2001	
Phase II		3Q2002	
Phase III		4Q2003	
Last PV/Last Visit			
US, EU, Japan Filing		4Q2005	
US, EU, Japan Approval		2Q2006	

Commercial

Base Case Forecast ($MM)



Financial Summary	U.S. ($MM)	WW ($MM)
Peak Sales ($MM)	$307	$189
Peak Standard Margin ($MM)	$275	$170
Peak Standard Margin (%)	89 6%	89 9%
Pre-Tax NPV @ 12 5% (global)	$464	

Product Profile (Efficacy, Safety, Convenience)

		Prob	Share Impact
Safety/AE	Addition of ABT-518 to cytotoxic regimen does not add significant side effects; side effects are similar to current gold std		
Conven	Oral, daily therapy		
Efficacy	Initial indication Approved to use in second line regimen in advanced patients in one medium/large cancer (e.g. breast, NSCLC, ovarian, NHL, or colorectal); In combination with cytotoxic therapies demonstrates clinically significant improvement in survival or time to tumor (or disease) progression compared to current gold standard in second line therapy		
Efficacy	Second indication (in year 3). Approved as a first line therapy in advanced patients in the same tumor type as initial indication with equivalent or marginally better efficacy compared to current gold standard.		
Efficacy	Third indication (in year 5). Approved as a second line therapy in a distinct tumor type, with equal or marginally better efficacy than current gold standard		
Other	US For patients with commercial insurance, ABT-518 will be covered with a minimal co-pay (<$35), Medicare will not reimburse for ABT-518 as a self administered medication; 75% patient compliance		

Commercial Profile	U.S.	Ex-U.S.
Launch Date	Q3 2008	Q1 2007
Price per Day at Launch (AWP)	$9,000 00 Similar to cancer, HIV, MS and transplant drugs	$4,500 00 Similar to cancer drugs
Sales force @ peak sales ($MM)	83	84
Promo @ peak sales ($MM)	66	65
COGS @launch, @ peak)	90% SMM	90% SMM
Market/Extensv/Other	Assumes 2% annual price increases	

Next Go/No Go — End of Phase I (early 2002)

Business Rationale — With ABT-518, ABT-510 and ABT-627, Abbott can establish itself as a clear leader in angiogenesis inhibition with 3 anti-angiogenesis drugs that act by alternative mechanisms The MMP-2 and -9 selectivity should allow for a larger therapeutic window and thus the potential for higher efficacy and lower toxicity than other MMPIs such as marimastat and prinomastat

Leeden EXHIBIT 37
FOR I.D. 4-26-07 JMK

Monthly Highlights – Key Project Progress

- Study initiation visits were conducted on 2/14 and 2/15.

Next Quarter's Key Progress Markers

Key Progress Markers	Target Date
• First patient enrolled	3/12
• Preliminary results from 6-week rat hepatotoxicity study	3/31
• Pre-IND meeting with FDA	6/1
• Preliminary results from 3-month rat chronic toxicity study	6/30

Key Project Issues and Risks

Risk or Issue	Potential or Known Impact (Check all that apply and describe impact)	Strategy / Actions	Area(s) Responsible	Resolution Date Planned / Actual
Identification of FDA requirements for cytostatic agents in oncology drug development.	☐ Cost ☐ Time ☐ Profile ☑ Regulatory	Phase I IND study to Transition program to solicit FDA input.	Clinical	6/1/01
Key tox finding was hepatotoxicity in one-month rat study. *In-vitro* and *in-vivo* data indicate a potential for mechanism based drug interactions.	☐ Cost ☐ Time ☑ Profile ☑ Regulatory	The Phase I first-in-man protocol has been designed to address these issues. A 6-week tox and metabolism studies have been completed. Results are under review. A 3-month rat toxicity study is ongoing.	Toxicology/ Metabolism	7/1/01

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ABBT 0000344

Key Project Issues and Risks

Risk or Issue	Potential or Known Impact: Check all that apply and Describe Impact	Strategy / Progress	Role / Responsibility	Resolution Date: Planned / Actual
As several competitors are in Phase II/III, ABT-518 product profile will need to demonstrate advantage over the other compounds (i.e., safety/efficacy)	☐ Cost ☐ Time ☑ Profile ☐ Regulatory	Ongoing analysis and comparison of competition throughout transition. ABT-518 has the potential to be the best in class compound. Pfizer (Agouron) announced 8/4/00 that they were stopping Phase III trials of prinomastat in advanced prostate and NSCLC because "primary efficacy objectives were not met". They are continuing trials in less advanced tumors, e.g., **glioma and NSCLC**, and will start trials in two additional tumor types. Efficacy was shown with marimastat in less advanced gastric cancer, but British Biotech announced on 9/27/00 that marimastat in combination with carboplatin was no better than carboplatin alone in advanced ovarian cancer. **Marimastat development was discontinued on 2/15/01.** Both the Pfizer compound and British Biotech's compound are hindered by dose-limiting joint toxicity.	Competitive Environment	
	☐ Cost ☐ Time ☐ Profile ☐ Regulatory			

Key Activities

Commercial

Activity	LBE	Actual
Market research to assess commercial potential of cancer types, both US and Ex-US.....	4/2001	
Assessment of patient compliance (for revision of forecast)	3/2001	
Assessment of off-label vs. spillover use (for revision of forecasts)	3/2001	
Assessment of cancer market growth (for revision of forecasts)	4/2001	
Assist with advisory planning	4/2001	
Development of brand and generic names	Late 2001	

Formulation Plan Date: 3/2000

Activity	Plan	Actual
Phase I Formulation	10/2000	
Phase II Formulation		
Formulation for Bio Study		
Phase III Clinical Supplies Manufactured		
NDA Lots (3) Completed		
Completion of 1 Year Stability for NDA		
Formulation Peer Review		

Drug Substance Plan Date: 3/2000

Activity	KG	Plan	Actual	Actual Projected Cost/kg
Chem Scien (GLP)	3.0/1.7	6/2000	6/16/00	$133,300
Chem Scien (GMP)	2.0/3.8	6/2000	6/29/00	$133,300
Chem Scien	15.0	6/2001		
SPD				
SPD				
SPD				
Demo Lot				
NDA Lot #1				
NDA Lot #2				
NDA Lot #3				
Validation Lot				

Toxicology Plan Date: 3/2000

Toxicology Activity	Planned Start	Actual Start Date	Report Completed
Gene Toxicology	5/2000		
Acute Studies	5/2000		
2-Week Monkey (non-GLP)	12/1999	12/14/99	
1-Month Rat (non-GLP screening)	12/1999	12/14/99	
1 Month Rat (GLP)	6/2000	6/27/00	
1 Month Monkey (GLP)	6/2000	6/29/00	
3 Month Rat	1/2001	1/2/01	
3 Month Mouse MTD			
SEG I and SEG II			
SEG III Rat (post natal development)			
6 Month Rat			
1 Year Monkey			
Carcinogenicity (2 yr) Rat			
Carcinogenicity (2 yr) Mouse			

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ABBT 0000346

All Clinical Studies:

Protocol Number	Phase	Study Name	Start 1st Pt. Dosed	End (Last CRF In)	Patients Target	Patients Current
M00-235	I	MD Study in cancer patients	2/28		40	
TBD	I	IND Study			20	

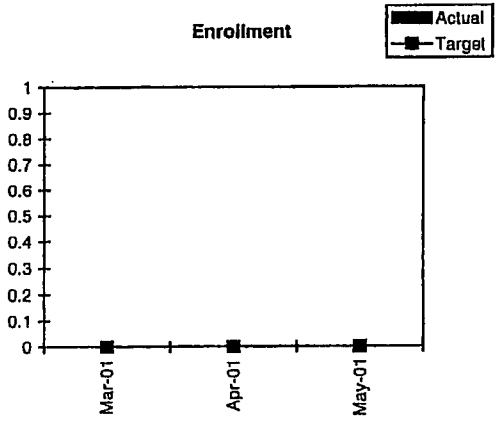
Protocol Number	Phase	Study Name	Start 1st Pt. Dosed	End (Last CRF In)	Patients Target	Patients Current

Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol:	**M00-235 - Phase I MD in cancer patients**
Objective:	**Determine MTD and safety profile in cancer patients**
ABT-518 Doses:	**25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day**
Comparator Doses:	**N/A**
Target Enrollment:	**40**
Status:	**Study initiated, clinical supplies delivered**
Major Findings:	

MXX-XXX – TITLE

(Author: Double click on chart to edit)



PLs' M

Abbott Portfolio Review

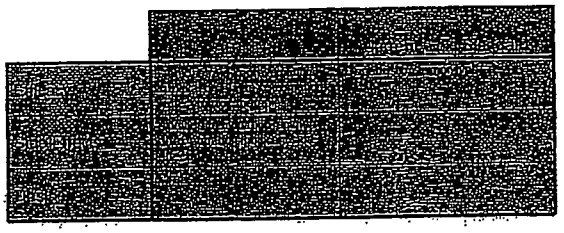
March 7-9, 2001

- Project ABT-518
- Compound Matrix Metalloproteinase Inhibitor
- Presenter Parry Nisen
- Project Team Members

A. Nabulsi (VH), T. Janus (MD), D. D'Amico (CPM)

ABT-518

- Target indication: Solid tumors
- Targeted unmet medical need: Cancer
- Target product profile vs. current gold standard:

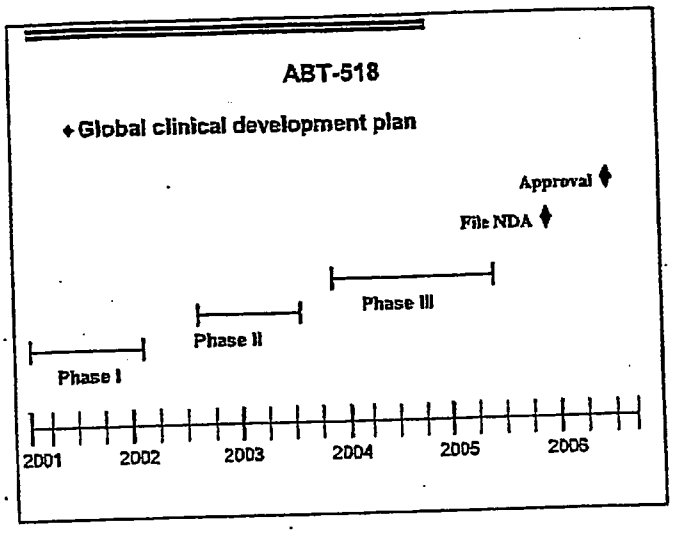


ABT-518

- **Key pre-clinical findings:**
  - **Pharmacology**
    - Potent and highly selective (gel-A and gel-B) MMP inhibitor
    - Anti-tumor activity seen in numerous murine cancer models
    - Inhibition of tumor growth is dose dependent
    - Blocks vessel formation in a mouse model of angiogenesis
  - **Pharmacokinetics / Metabolism in animals**
    - Sustained plasma concentrations following single-dose in monkeys
    - Oral bioavailability between 68 and 93% in animals
    - Multiple metabolites are produced after repeat dosing in rats and dogs
  - **Toxicology**
    - No meaningful effects in genotoxicity, cytotoxicity or ligand binding assays
    - No remarkable cardiovascular effects in dogs
    - Steatosis seen in high-dose rats two weeks after drug stopped

ABT-518

- **Chemistry and Manufacturing**
  - **Drug substance**
    - Six steps from commercial starting materials
    - 3-month turnaround time to manufacture
    - Manufactured at Abbott
  - **Drug product**
    - Neat drug in a capsule (25 and 200 mg) for Phase I
    - Hand-fill or semi-automation at a third party manufacturing facility (Phase I)
    - Formulation development work will begin post Phase II Go/No Go decision


ABT-518
Global clinical development plan
Approval
File NDA
Phase III
Phase II
Phase I
2001
2002
2003
2004
2005
2006

ABT-518

- Clinical development budget

Phase	Funding ($MM)
Pre-Clinical	5
Phase I	12
Phase II	47
Phase III	78

ABT-518

- **Phase I study:**

  Multiple-dose study in patients with advanced cancer

  - Objectives
    - Establish safety profile
    - Determine the maximum tolerated dose (MTD)
    - Assess PK
    - Determine Phase II dose
  - Design
    - 28 days + extension
    - Single-dose of drug administered on Day 1; resume dosing (daily) on Day 4
    - Approximately 40 patients; 3 patients per dose
      - Add 6 or more patients at MTD to collect additional safety information
    - Doses: 25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day

ABT-518

- **Phase I plan:**

  IND Study

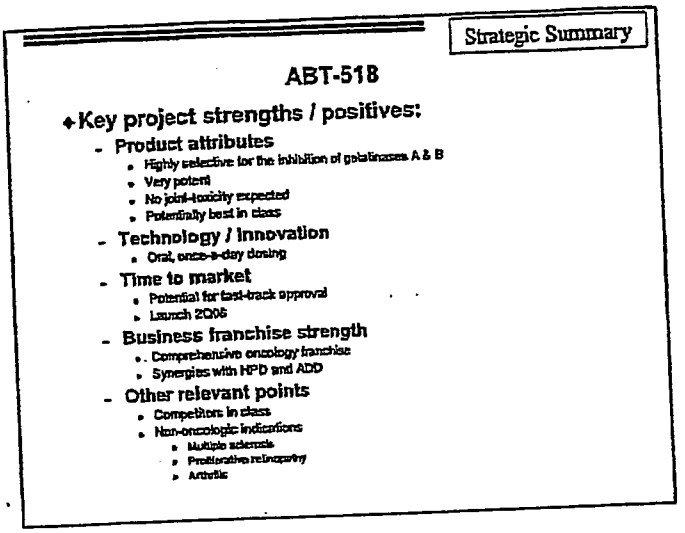
  - Objectives
    - PD-guided Phase II dose selection
    - Long-term safety
  - Design
    - Multiple dose escalation study
    - Assess MMP activity in accessible tumors
      - Melanoma
      - Head and Neck Cancer
    - Approximately 20 patients

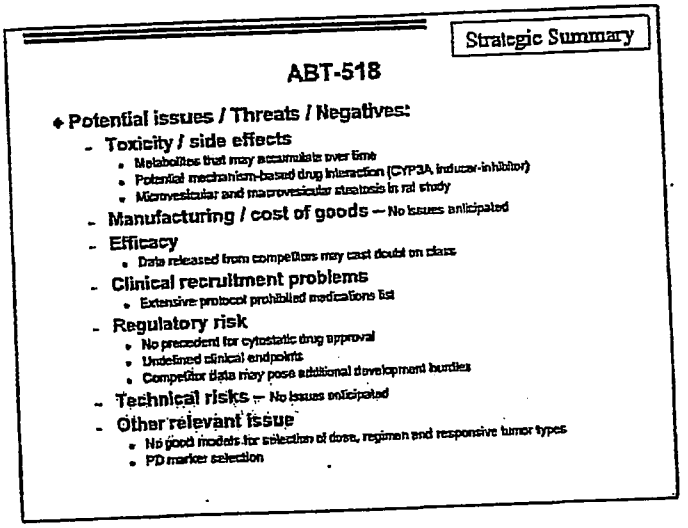
ABT-518

- **Phase II development plans:**
  - 3 Studies
    - 3 Tumor types as defined by Phase I and animal efficacy
    - 150 patients per study
  - Dose finding
  - Assess safety issues identified in Phase I
  - Thirteen month duration

ABT-518

- **Phase III plan:**
  - Demonstrate improvement in survival or TTP in combination with cytotoxic therapies





Strategic Summary

ABT-518

- **Key decisions:**
  - Important upcoming decisions
    - Transition team Go/No Go Phase II - 12/01
  - Proposed budget (2001, and all years to launch)

Year	R&D per year ($MM)
2001	7
2002	38
2003	36
2004	29
2005	23
2006	8

Strategic Summary

ABT-518

- **Key decisions:**
  - Evaluate safety at multiple doses and dose regimens
  - Dose and regimen selection for Phase II
  - Tumor type selection for Phase II
  - Clinical trial design to demonstrate efficacy

Strategic Summary

ABT-518

- **Proposed action plans**
  - **Manufacturing**
    - Initiate formulation work post Phase II Go/No Go
  - **Nonclinical**
    - Additional toxicology and metabolism studies are underway to explore the CYP3A and steatosis issues
  - **Clinical**
    - Measure metabolites in Phase I
    - Assess bioactivity via PD markers in Phase I
    - Hold a Pre-IND meeting with the FDA to discuss endpoints
  - **Contingency plan**
    - Pursue alternative indications
      - Multiple sclerosis
      - Proliferative retinopathy
      - Arthritis

PLs' N

MMPI MONTHLY MEETING AGENDA
3/8/2001, 10:30-12:00, AP6A-1A
Objectives: To Review MMPI Project Status

- B.H. PRE-IND TIMELINE
- TJ PK VALIDATION

* Ask if PD data will ever be submitted. If so, audit.

NOTES

6/20 Kevin – No

I. Clinical – A. Nabulsi/ D. D'Amico

VERHEADS ø

- Leiden portfolio review 3/7
- M00-235 sites initiated 2/14 & 2/15
- Drug shipped 2/28 & 3/1
- First patient: Monday (3/12)
- IND timeline being revised (Mtg 3/9)

(I) HOW CAN WE CONTINUE IF COMPETITION IS DROPPING OUT? PRE-CLINICALLY WE DIFFER. COMP TO LOW DOSES, MONO- VS COMBO, SKIPPED PH II, NOT RIGHT STAGE TUMORS
→ WE'LL LOOK @ ASCO & AACR FOR COMP INFO
→ WE'LL KNOW IN 3-6 MO WHERE WE'LL STAND
TODD LEAVES FOR AACR BY APR 22nd – HE'LL LOOK @ ABSTRACTS UPON
→ VANDERBILT TELECONFERENCE ON 3/12 TO DISCUSS THE IND STUDY
* FIND OUT CANCER TYPE FOR 1ST PATIENT

II. Toxicology – L. Loberg

VERHEADS |||

- 6 week rat study completed
- 3 month rat – 1st necropsy 4/10/01

(II) 3 MONTH: In high dose group ↓ body weight gain, dehydration, alopecia; similar results to previous study 070

6 wk: Inlife done, necropsy all, assembling data on mitochondrial assays; High dose group did recover body weight and ↑ food consumption after off drug

Talk in vitro data plus data from the study & 070 & give results by next mtg

- Is there a CNS involvement? Bill Bracken
  ↳ concerned w/ ↓ body weight; possibly not just 2° ↓ food.

III. PK – B. Carr/ M. Rieser/ Tawakol

VERHEADS ø

- PK method validation in human plasma is complete for all 7 analytes. (report not written yet)
- Finishing re-analysis of metabolites from toxicology studies (last fall).

(III) Call site w/ Matt & Tawakol to discuss status their validation
Needed for IND. When will be available? Bill Bracken on top of it.

IV. PARD – J. Cannon/ T. Garavalia

VERHEADS ||

- Capsule update: Feton run at MDS Pharma) completed; 200mg capsules; 73% yield
- Next finishing run scheduled for 6/01

(IV) – Standard Deviation of empty capsule > than expected
– Drug behaved differently when filling the capsules
– 300 rejects → Use for development work. Must be designated "experimental." Next time – will incorporate rework steps for GMP run.
– June run @ MDS 2° IDC facility booked
– ALERT Cmc stability update, pitting, drug in bottle [illegible]

V. CAPD – S. Wittenberg

- No Update

VI. Discovery – S. Davidson

- No Update

VII. Metabolism – D. Hickman

- No Update

VIII. Next Team Venture Meeting

When: Thursday, April 12, 2001
Where: AP6A-1A
Time: 10:30 – 12:00

PLAINTIFF'S EXHIBIT
D'Amico 27
11/28/06

PLs' R

Philip M Deemer
03/12/2001 03:03 PM

To: sblewitt@jhancock.com@internet
Subject: MMPI Program Update

John Leonard looked at all of the documents one last time in preparation for execution and noted an oversight on one of the Programs. On the ABT-518 program, he noted that Phase I was to have started on December 2000 (4Q2000) but in fact did not start until earlier this month. This pushed the timeline back by a quarter throughout but the launch date is not affected and is actually planned one quarter earlier (2Q06). Steve, as you know the timing of starting some of these earlier compound studies is related to completing this financing and hence the reason this one got pushed back a little.


ABT-518 0301.doc


ABT-518 0301.WK4


ABT-518 0301.xls

PLAINTIFF'S EXHIBIT
Leonard 27
11/30/07

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ABT - 518

Descriptive Memorandum

February 2001

Abbott Laboratories

MMPI

Overview

Abbott's Matrix Metalloproteinase Inhibitor (MMPI) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases. This more "chronic" approach to therapy has the potential to transform cancer into a disease that patients live with, much like the effect of HIV protease inhibitors on patients with AIDS. It also has the potential to expand the cancer market significantly by increasing the average length of treatment and expanding the pool of patients eligible to receive therapy.

The MMPs comprise a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

MMP inhibitors (MMPIs) may suppress the progression of tumors by several mechanisms:

- Suppress invasion/metastasis by blocking the membrane traversal and access to blood/lymphatic vessels
- Blocking the remodeling of extra-cellular matrix in the vicinity of primary tumors to prevent stroma-bound growth factors from stimulating tumor growth
- Blocking angiogenesis by preventing the proliferation and migration of endothelial cells and neovascularization of tumor.

Experimental evidence suggests that gelatinase A and gelatinase B are particularly important in tumor progression, consequently the project team has targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes a dose-limiting side-effect characterized by severe joint pain and stiffness. Since these joint effects may be mediated by inhibition of other MMPs like fibroblast collagenase, highly gelatinase selective agents may be efficacious without producing dose-limiting side effects.

The MMP selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds. ABT-518 possesses sub-nanomolar inhibition potencies versus both gelatinase A and gelatinase B and is substantially more selective for the inhibition of the gelatinases over fibroblast collagenase than marimastat and prinomastat. Despite its high selectivity, ABT-518 demonstrates antitumor activity equal or superior to prinomastat: Inhibition of tumor growth is dose dependent in both syngeneic and xenograft models. ABT-518 is also effective in blocking vessel formation in a mouse model of angiogenesis. ABT-518 is a stable crystalline solid which can be synthesized in six steps (25% overall yield) from commercial starting material.

ABT-518 gives rise to sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailabilities range between 68 and 93% depending on formulation and species. Several metabolites are produced after repeated oral dosing of ABT-518, although their relative amounts varies with gender and species.

ABT-518 displays no meaningful effects in genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. ABT-518 produces no significant toxic effects in rats treated with 100 mg/kg/day over 28 days. Plasma concentrations generated by ABT-518 in these studies are at least 20-fold higher than those necessary to produce efficacy in cancer animal models. ABT-518 is therefore a compelling development candidate with the potential to

demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials. Phase 1 clinical trials in cancer patients began March 2001.

The market

Currently, cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market.

Global Sales by Market Segment ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Sales by Region ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the MMPI will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, MMPIs will probably be adopted initially as add-on the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast

Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL

Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian

Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas

Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Compounds in Development

The MMP inhibitor field is competitive. More than 30 firms have filed patents claiming small molecule MMP inhibitors over the past 5 years, and several companies have compounds in advanced clinical development. Abbott's compound may be 3rd or 4th to market and will have to demonstrate a competitive advantage to gain the share necessary to support the clinical development of this compound. Companies with compounds in advanced clinical development for the treatment of cancer include Agouron/Warner Lambert/Pfizer, British Biotechnology/Schering Plough and BMS and are listed below. Other companies are targeting this mechanism for arthritis.

MMPIs in Clinical Development for Cancer

Compound	Company	Comments	Phase
Marimistat	BritishBiotechnology/ Schering Plough	Broad spectrum, dose limiting toxicity. Activity seen in gastric cancer, but negative results in pancreatic.	III
Prinomastat	Agouron/ Warner Lambert/ Pfizer	Moderate gelatinase selectivity, dose limiting toxicity. May be dosing sub-optimally to avoid toxicity. Efficacy data not available.	III
BMS 275291	BMS	Broad spectrum, joint effects seen in Phase I studies.	II

Bayer recently dropped development of BAY 12-9566 due to concerns about potential toxicity. Recent results from a study with marimistat in pancreatic cancer, where adding marimistat to Gemzar resulted in no survival advantage, has led to speculation that MMPIs may be more applicable in less aggressive cancer types or earlier stages of the disease. Alternatively, it could be a reflection of the inability to examine higher doses of marimastat due to joint effects.

The joint effects produced by the compounds listed above almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy. Any MMP inhibitor that lacks these side effects will possess a substantial competitive advantage. The musculoskeletal effect produced by marimastat and prinomastat in cancer patients is typically described as arthralgia, myalgia and tendinitis, which occurs predominately in the upper limbs. While mild cases respond to analgesics, interrupting therapy for a period of approximately 2 weeks is necessary when the condition is less well tolerated.

Although Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class.

Product profile

The objective of a product profile at this time in the product's development is to provide a target for the types of attributes that will be required to be commercially successful. This profile is based on market research with oncologists and consultation with opinion leaders. This profile will continue to be refined as more is known about this product's profile, development of competitive products and the market continues to evolve.

	Base	Optimal
Efficacy	ABT-518, alone or in combination with best therapy, provides at least one of	Provides more than one of the efficacy benefits outlined.

	the following benefits in at least one solid tumor type: • Increased survival • Tumor regression • Improved quality of life • Increased time to tumor/disease progression	
Competitive advantage	ABT-518 will need to demonstrate a clinically significant advantage in efficacy (see parameters above) or additive synergistic activity with current/competitive agents or clinically significant advantage in side-effect profile relative to other MMPI agents.	Same
Administration	Convenient administration relative to competitive agents.	Same plus reimbursement in US market.
COGS	A finished cost of goods that is consistent with at least an 80% standard manufacturing margin.	A finished cost of goods that is consistent with at least a 90% standard manufacturing margin.

Marketing overview

Product Usage: Physicians have indicated that they would use MMPIs initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. The MMPI was regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy.

Product Benefits/Efficacy: Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. The MMPI mechanism has more recently been implicated as having an even more active role in cancer pathogenesis, from preventing primary tumor growth to anti-angiogenic properties. Positive results from competitive agents, such as marimistat in gastric cancer, provides proof of principle for this mechanism.

Side Effects: The proposed safety profile of MMPIs (excluding joint toxicity) may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, MMPIs may *have* to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance. As the 3rd or 4th MMPI to market, SE hurdles will be even higher for this compound. As a critical Go/No Go decision point, the joint toxicity of this compound will be evaluated in an expanded Phase I multi-dose study.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are acknowledged by physicians and patients as being more convenient to the patient. Chronic oral dosing may also reduce overall costs, as infusion support products and personnel would not be required, enhancing pharmacoeconomic evidence.

COGS: Initial estimates on finished cost of drug suggest that drug costs will not be significant for this compound

Off-label use: Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

Competition: As the 3rd or 4th MMPI to market, Abbott's compound will need to demonstrate a meaningful clinical advantage over compounds that are in more advanced development. Strict Go/No Go criteria will determine if the MMPI can meet these hurdles. If they cannot be met, the compound will not move forward.

Development/Regulatory: With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several MMPIs in late stage development, Abbott can learn from their experience.

Other Approaches: Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

Pricing: The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. However, as an oral therapy in the US market, there may be additional downward price pressure for this agent. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are preferred by physicians and patients because of the convenience to the patient. However, this form may not be the best choice for some people who already have certain digestive system symptoms (vomiting, diarrhea, or severe nausea), cannot swallow liquids or pills, or cannot remember when or how many pills to take. Additionally, in the US market there are several unique factors that currently do not favor oral therapies. Novel oral therapies are not currently reimbursed by Medicare, a significant payer for the oncology patient population. Also, 40-60% of a community oncologist's income is generated through the administration of IV drugs. An oral therapy would not be a source of revenue to the physician.

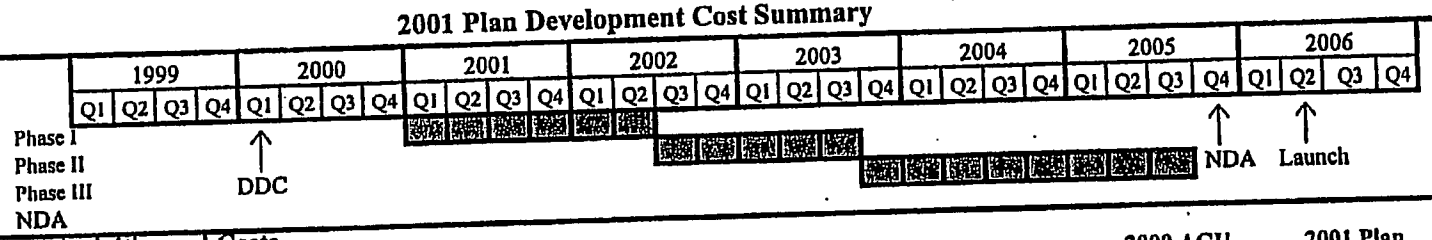
Clinical Studies

Clinical studies across a wide range of solid tumors will be initiated, including but not limited to breast cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, etc...

Final indications pursued will depend from the results of the phase II studies.

MMPI (ABT-518)
2001 Plan Development Cost Summary

Program Status



Major Development Activities and Costs	Total Patients	Enrolled as of 8/00	Start	End	2000 AGU Cost	2001 Plan Cost
Clinical Program					$300	$769
Multiple Dose in Cancer Patients	40	...	1Q/01	1Q/02	...	$500
IND Study	14	...	3Q/01	1Q/02	...	$108
Other Studies / EVR					$70	$65
Phase-I Center / PK					$778	$754
Venture Management					$57	$118
Data Management/Statistics					$1,205	$2,314

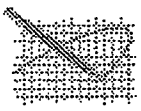
Chemistry, Manufacturing, and Controls (CMC)	2000 AGU	2001 Plan
Formulation / Analytical	$546	$1,031

Drug Safety Support	2000 AGU	2001 Plan
Ongoing Drug Safety support	$1,681	$2,125

Other Support Costs		
Discovery	$1,447	$1,348
Medical Affairs	$5	$20
Regulatory Affairs / Research Quality Assurance	$26	$39
Other / In-licensing Fees	$90	$123
Total Program	$5,000	$7,000

ABBT 0004039
CONFIDENTIAL

PLs' T



Diane L
D'Amico /LAKE/PPRD/ABB
OTT
03/12/2001 04:49 PM

To jhm@nki.nl
cc E.E.Voest@azu.nl, Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject Re: M00-235 Update

Dear Professor Schellens:

I forwarded your request to Dr. Nabulsi who will contact you tomorrow morning.

Kind regards,

Diane

jhm@nki.nl on 03/12/2001 04:26:39 PM

jhm@nki.nl on 03/12/2001 04:26:39 PM

To: diane.damico@abbott.com
cc: e.voest@azu.nl, jhm@nki.nl, E.E.Voest@azu.nl
Subject: Re: M00-235 Update

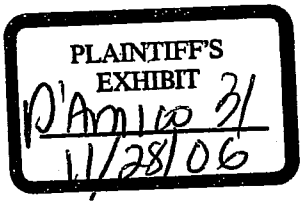
..I would like to have asap the name and address for correspondence of the highest ranking officer at Abbott responsible for this project and the decision of today.

Jan Schellens
----- Original Message -----
From: Diane D'Amico <diane.damico@abbott.com>
To: <jhm@nki.nl>
Cc: Robert Hansen <Robert.Hansen@ln.ssw.abbott.com>; Diane Bronson <Diane.Bronson@ln.ssw.abbott.com>; Azmi Nabulsi <Azmi.Nabulsi@ln.ssw.abbott.com>; Lori Rountree <Lori.Rountree@ln.ssw.abbott.com>; Paige Gjelsten <Paige.Gjelsten@ln.ssw.abbott.com>; Todd Janus <Todd.Janus@ln.ssw.abbott.com>; Willy Jansen <Willy.Jansen@add.ssw.abbott.com>; Else Meijer <Else.Meijer@ln.ssw.abbott.com>; Jim Looman <Jim.Looman@ln.ssw.abbott.com>; <idvl@telescan.nki.nl>; <j.maaskant@telescan.nki.nl>
Sent: Monday, March 12, 2001 10:09 PM
Subject: M00-235 Update

Dear Professor Schellens,

As you know, we have been instructed to halt the M00-235 study. I assume that you know that the AZU enrolled a patient into the study today.

At this time, we have instructed the AZU to proceed with the M00-235 patient per the protocol until they hear from us otherwise. We hope to have further instructions by tomorrow (Tuesday, 13Mar01).



31

We ask that you refrain from enrolling any additional patients at your site at this time.

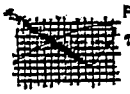
Thank you for your patience and understanding in this matter.

Best regards,

Diane

PLs' V

MAY. 31. 2005 11:31AM NO. 3057 P. 5



Paige Gjelsten
13-03-2001 21:25

To: Jim Lorman/HDOFDDORP/AI/ABBOTT@ABBOTT, Willy Janssen/HDOFDDORP/ADD/ABBOTT@ABBOTT, Elsa Meijer/HDOFDDORP/AI/ABBOTT@ABBOTT
cc: Diane L D'Amico/LAKE/PPRD/ABBOTT@ABBOTT, Todd J Janus/LAKE/PPRD/ABBOTT@ABBOTT, Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT, Lori V Rountree/LAKE/PPRD/ABBOTT@ABBOTT, Diane C Bronson/LAKE/PPRD/ABBOTT@ABBOTT, Robert Hansen/LAKE/PPRD/ABBOTT@ABBOTT
Subject: M00-235 Study Hold Lifted

I just want to let you know that the M00-235 study hold has been lifted. Prof. Schellens and Prof. Voest have been contacted. As we gather more information, we will keep you informed.

Kind regards,

Paige

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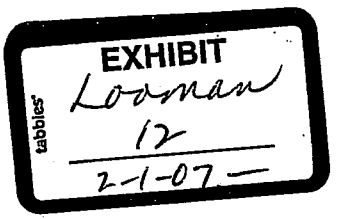


PLs' X

Diane L. D'Amico /LAKE/PPRD/ABBOTT
03/14/2001 12:53 PM

To Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT
cc Lori V Rountree/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject Per Your Request

Azmi:

It is my understanding that the following chain of events led to the erroneous dosing of one patient in Abbott Study M00-235 (MMPI):

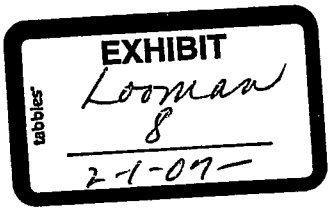
Friday, March 9 5:45 PM (CST)
Dr. Nabulsi learned that the M00-235 should be put on hold.

Sunday, March 11 10:00 AM (CST)/1700 (CET)
Dr. Nabulsi phoned Jim Looman (Associate Director, EVR Netherlands) to tell him that the M00-235 study should be put on hold. Jim Looman was instructed to contact both Dr. Schellens and Dr. Zonnenberg to notify them of the hold.

Monday, March 12 0900 AM (CET)
Jim Looman phoned Dr. Voest (Dr. Zonnenberg's superior) and alerted him to the hold on the study. The call lasted approximately 10 minutes. The patient was dosed at 0937 (CET) by Dr. Laurens Beerepoot (a sub-investigator). It appears that Dr. Voest was not able to notify Dr. Beerepoot in time. It is probably safe to assume that the patient was already at the site for Day 1 study activities at the time of the call.

Monday, March 12 0910 AM (CET)
Jim Looman phoned Dr. Schellens to notify him of the study hold. Schellens was not available to take the call. Jim then contacted Jolanda Maaskant (site QA officer) and alerted her to the study hold. The site sent home a patient who was waiting to enroll.

Diane



PLs' Z

Jim
Looman/HOOFDDORP/AI/
ABBOTT
03/19/2001 09:31 AM

To Diane L D'Amico/LAKE/PPRD/ABBOTT
cc
bcc
Subject Re: M00-235 Update

Agree, and what I mean is: if the docs have confirmed with Azmi that it is OK to schedule patients they will issue that to their Staffs, but they are currently dormant for that answer. Since Voest and Schellens are in the States I assume that this will be discussed at the sites locally later this week. I have asked Else and Willy to kindly ask for a planning of new patients with the sites. Please check with them to verify,
kind regards,
Jim
Diane L D'Amico

Diane L D'Amico
03/19/2001 03:40 PM

To: Jim Looman/HOOFDDORP/AI/ABBOTT@ABBOTT
cc:
Subject: Re: M00-235 Update

Dear Jim,

Yes, I figured that the sites might be a bit gun-shy about enrolling patients into the study. I assumed we would not get any patients today but maybe by next week Monday(26Mar01).

Are you indicating that the sites are "dormant" until Schellens/Voest speak with Azmi at AACR? If so, that might mean we would not get any more patients until 2Apr01. Azmi did speak to all three docs (Schellens, Zonnenberg and Voest) on the phone last week with a clear message of "Go".

Best regards,

Diane

Jim Looman

Jim Looman
03/19/2001 04:07 AM

To: Diane L D'Amico/LAKE/PPRD/ABBOTT
cc: Else Meijer/HOOFDDORP/AI/ABBOTT@ABBOTT, Paige Gjelsten/LAKE/PPRD/ABBOTT@ABBOTT, Todd J Janus/LAKE/PPRD/ABBOTT@ABBOTT, Willy Jansen/HOOFDDORP/ADD/ABBOTT@ABBOTT
Subject: Re: M00-235 Update

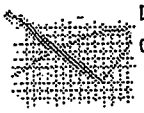
Hi Diane,

yes we are hoping for a "milder" week. Azmi is currently with Prof. Voest in New Orleans to discuss the re-start of the study and he would personally phone with Prof Schellens. In the meantime Else and Willy and vigilant to see if there is anything they can do at this moment, but the overriding message from the sites is that they are "dormant" for the final re-start resolution after discussions of Azmi with the PI's. If we hear anything else from this end we'll let you know,

kind regards,
Jim

EXHIBIT
tabbies
Looman
17
2-1-07

Diane L D'Amico



Diane L D'Amico —— 03/16/2001 07:30 PM

To: Else Meijer/HOOFDDORP/AI/ABBOTT@ABBOTT, Willy Jansen/HOOFDDORP/ADD/ABBOTT@ABBOTT, Jim Looman/HOOFDDORP/AI/ABBOTT@ABBOTT
cc: Paige Gjelsten/LAKE/PPRD/ABBOTT@ABBOTT, Todd J Janus/LAKE/PPRD/ABBOTT@ABBOTT
Subject: M00-235 Update

Dear Jim, Willy and Else,

What a long week this has been! Not only was this week long, but it was filled with ups and downs. Todd, Paige and I came in Monday morning to learn that the MMPI project had been put on hold. The next day, we learned that the hold had been lifted. I just hope that next week will be a little less eventful. :)

On a high note, one patient was enrolled into the study. Congratulations! As you can imagine, we (the MMPI Team) are very excitied about pulling out in front of the TSP Team (all in good fun). We haven't heard any news on the patient, so we assume that "no news is good news". Presumably the patient was released today.

Did Dr. Schellens receive his Board of Director Approval? I know it was expected on the 14th, but we haven't received anything to indicate that the approval was granted.

A teleconference is scheduled with Dr. Hilde Rosing next week Tuesday to discuss the status of their PK validation. The Abbott PK Team did successfully validate their PK method, so our back-up is in place should it be needed. We are still optimistic that Dr. Rosing's team will validate soon and be ready for processing the PK samples.

Dr. Beerepoot sent some results to me this week from his PD validation work. The Abbott PD team is reviewing what Dr. Beerepoot sent. Dr. Beerepoot reported that he would have more results this week. So, this is moving along slowly but surely. No need to push at this time.

That seems to be it for this week. Please keep us posted on any enrollment activities next week.

Kindest regards,

Diane

P.S. Both Todd and I will be out the entire week of March 26, so please direct all issues to Paige.

PLs' AB

Philip M Deemer/LAKE/CORP/ABBOTT

03/20/2001 09:53 AM

To Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT
cc
bcc
Subject Hancock and Alcon

You probably heard that Hancock was signed last week $214,000,000 over 4 years! A long time coming but finally done. We had a little scare at the end when it looked like 518 was being slowed down which could have been the deathnell to the deal I worked with John to protest that and I understand it is back on track.

On another matter, Alcon called me looking for 2g of 839. We don't need to work with them if there is no/little synergy. I told them I thought it would be difficult to give them that amount at this time but that I would check with you.

Perry, We should catch up with one another before too long

Best regards.

PLs' AC

Jim Looman
03/21/01 09:32 AM

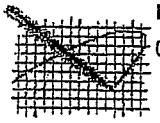
To: Diane L D'Amico/LAKE/PPRD/ABBOTT, Paige Gjelsten/LAKE/PPRD/ABBOTT@ABBOTT
cc: Else Meijer/HOOFDDORP/AI/ABBOTT@ABBOTT, Todd J Janus/LAKE/PPRD/ABBOTT@ABBOTT, Willy Jansen/HOOFDDORP/ADD/ABBOTT@ABBOTT, Lori V Rountree/LAKE/PPRD/ABBOTT@ABBOTT, Azmi A Nabulsi/LAKE/PPRD/ABBOTT
Subject: Restart 518 study

Dear Diane/Paige,

In order to re-start **all** activities for 518, we need the word from Azmi that he has received confirmation from both PI's that they are OK with the re-start and that they have also instructed their staffs to re-start. At the moment our site contacts are telling us that they are waiting for this official confirmation and would like to wait to do anything before that.
I have asked Else and Willy to **kindly** request if there are things that we could do in parallel in the meantime, but I would like to ask all of the team not to start pushing now before we have officially resolved the hold-situation. This applies to e.g. requests for getting documents, enrollment planning etc.

I am confident that we are all in agreement that the re-start should be done in the best possible way. In my view we should first get the buy-in from the PIs and then re-activate the supporting personnel.
Please keep us informed on the progress of **your** contacts with the PI and staff.
kind regards,

Jim
Diane L D'Amico



Diane L D'Amico
03/21/2001 12:01 AM

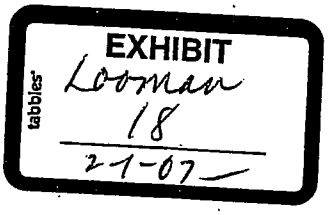
To: Else Meijer/HOOFDDORP/AI/ABBOTT@ABBOTT, Willy Jansen/HOOFDDORP/ADD/ABBOTT@ABBOTT
cc: Jim Looman/HOOFDDORP/AI/ABBOTT@ABBOTT, Todd J Janus/LAKE/PPRD/ABBOTT@ABBOTT, Paige Gjelsten/LAKE/PPRD/ABBOTT@ABBOTT
Subject: M00-235 Enrollment

Dear Else and Willy,

Have you heard from either M00-235 sites what their enrollment plans are for the rest of the 25mg cohort?

Best regards,

Diane



PLs' AP

Diane L D'Amico /LAKE/PPRD/ABBOTT
05/25/2001 03:52 PM

To Lise I Loberg/LAKE/PPRD/ABBOTT@ABBOTT
cc Diane C Bronson/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject Re: ABT-518 Tox

Lise-

Maybe you read the email below wrong. Can we wait until Diane says Yes/No? I don't want you to start something that is still on hold.

Thanks,

Diane

Lise I Loberg

Lise I Loberg
05/25/01 03:23 PM

To: Diane L D'Amico/LAKE/PPRD/ABBOTT@ABBOTT
cc: Diane C Bronson/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Re: ABT-518 Tox

Will do!
Diane L D'Amico

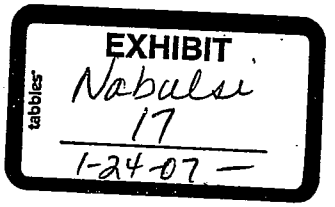
Diane L D'Amico
05/25/01 03:01 PM

To: Diane C Bronson/LAKE/PPRD/ABBOTT@ABBOTT
cc: Lise I Loberg/LAKE/PPRD/ABBOTT@ABBOTT
Subject: ABT-518 Tox

Diane,

Can Lise proceed with any of the ABT-518 activities that were previously put on hold (i.e., very long chain fatty acid sample analysis from the 6-week rat study and histopath from the 3-month rat study)?

Diane



PLs' BL

Timeline of events occurring with Study M00-235 in the Netherlands

14 february 2001	Site initiation Schellens, Amsterdam
15 february 2001	Site initiation Zonnenberg, Utrecht
7 march 2001	Nisen (DVP, Oncology, Abbott US) and Nabulsi (Oncology head, Abbott US) attended Abbott senior management review: "concern regarding the continuation of ABT-518 development"
11 march 2001	Nabulsi (Oncology head, Abbott US) calls Looman (ass. Med Dir Oncology, Abbott NL) to inform about immediate stop ABT-518 project (and thus study M00-235). Janus (Med. Dir Oncology, Abbott US) and D'Amico (PM, Oncology, Abbott US)
12 march 2001	Looman calls Schellens and Zonnenberg and requests to NOT enroll any patients due to decision Abbott to stop study Zonnenberg has enrolled patient 1001; Schellens did not enrol a patient awaiting BoD approval D'Amico sends Beerepoot (sub-I, Utrecht) memo to allow continuation with pat 1001 and await further news (expected on 13 Mar 01); no new patients to be enrolled. Schellens also informed by memo (D'Amico).
13 march 2001	Abbott informs Schellens and Zonnenberg that study hold has been lifted.
23 march 2001	1001 stops study due to DP (and dies on 30 apr 01 due to cerebral mets)
26 march 2001	Schellens enrolls Pat 1002
23 april 2001	Zonnenberg enrolls pats 1003 & 1004
25 april 2001	Pat 1002: SAE (dyspnea/pleural effusion), probably not related
12-16 may 2001	ASCO: discussion by Abbott and sites: no safety issues: go to level 2 (50 mg)
18 may 2001	Memo Janus confirming escalation to level 2 (50 mg) per 21 May 2001
21 may 2001	Pat 1002 withdraws consent (due to SAE) Start patient first patient on 50 mg at NKI - 1101 JDE
22 may 2001	Start AE of 1004 (day 29 of study) - Rise of Creatinin: possibly related
25 may 2001	Hospitalization pat 1004: AE → SAE
25 may 2001	Initial SAE report pat 1004 to Abbott Safety Desk: relationship: possible related due to rising creatinin: DLT
26 may 2001	Stop medication pat 1004 to allow decrease of toxicity to within one level of baseline
30 may 2001	Follow-up SAE report; relationship: possible caused by kidney failure
30 may 2001	Zonnenberg sends letter to EC regarding pat 1002 reporting SAE: relapse pleural effusion needs to be changed into dyspnea
1 june 2001	MMPI project (ABT-518) deemed a No/Go by senior management
5 june 2001	Teleconference Abbott – Zonnenberg: relationship SAE 1004 is still possibly related, but needs to be probably not related, if enrollment of new patients at level 2 (50 mg) can continue. Schellens; 2nd patient 1102 NKI is waiting to be included. Decision Abbott to suspend enrollment to clarify renal toxicity, based on suggestion by Zonnenberg. Patient 1004 stops study due to SAE
12 june 2001	Verbal announcement of Abbott (Nabulsi) to stop study to Schellens and Zonnenberg
14 june 2001	Teleconference with Voest to officially inform him of study termination
19 june 2001	1003 stops study due to DP
21 june 2001	Teleconference with Schellens to officially inform him of study termination After this call, an official study termination letter was sent to Schellens and Zonnenberg
22 june 2001	Receipt of registration form of proposed 2nd patient at 50 mg by Schellens
22 june 2001	Memo Janus: relationship SAE 1004 will be changed to: probably not; Schellens to announce 2nd patient at 50 mg; official paperwork from Zonnenberg to confirm changed relationship pending

25 june 2001	2nd patient at 50 mg included 1102 by Schellens, however no documentation of changed relationship received from Zonnenberg. Patient should have received 25 mg due to possible DLT
26 june 2001	Visit Nabulsi to both sites to explain termination of study
6 july 2001	Conference call with Schellens asking him to not enroll new patients at 50 mg; Statement from Schellens that no more patients as of 6 Jul 01 except for pat 1101 have been enrolled at 50 mg
7 july 2001	Memo Janus to indicate that relationship has not changed, so any new patient should receive 25mg.
11 July 2001	Memo of datanurse of Zonnenberg signaling unawareness of changed relationship from probably not back to possible
12 july 2001	Renewed request to Schellens to confirm that no new patients after pat 1101 have been enrolled; Additional information received by Janus about inclusion of second patient 1102 on 25 June 01
25 july 2001	Memo from Schellens to inform Abbott that patient 1102 will continue on 50 mg, no drug related toxicities.
27 july 2001	Memo Knight (PM, Abbott Oncology US): Nabulsi agrees with proposed strategy by Schellens. Protocol deviation noted and will be reported correctly.
31 july 2001	Zonnenberg letter to Janus: Relationship SAE pat 1004 remains possibly related; recommendation Zonnenberg to add 3 more patients @ 25 mg.
10 dec 2001	Zonnenberg sends corrective letter to EC to change description of SAE pat 1002 from "relapse pleural effusion" to "dyspnea". Content and outcome SAE have not changed.
30 nov 01	Close out visit Schellens
11 dec 2001	Close out visit Zonnenberg

PLs' BY

James W Thomas
[redacted]
12/21/99 08:06 AM

To: Fred W Siebert/LAKE/PPRD/ABBOTT@ABBOTT, Kevin J Heuser/LAKE/PPRD/ABBOTT@ABBOTT
cc: (bcc: James W Thomas/LAKE/PPRD/ABBOTT)
Subject: 114 Sample Size

Below is my attempt at writing up the sample size section of the 114 protocol.

This study is designed to enroll approximately 320 patients (80 patients in each treatment group). This sample size will allow for the detection of a 0.46 effect size in the average Daily Pain Intensity score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two- tailed Type I error) level with at least 80% power. This calculation is based on results obtained from ABT-594 study M99-833 and published data using Gabapentin for patients with painful diabetic polyneuropathy (add reference here to Dec 1998 JAMA article) and assuming an 39% and 25% improvement from baseline for ABT-594 and placebo respectively.

Jim

Thomas DEP. EX. NO. 1
FOR ID., AS OF 4/13/07

PLs' CC

CONFIDENTIAL

ABT – 594

Descriptive Memorandum

April 2000

Abbott Laboratories

ABT-594

Opportunity Overview

ABT-594 (the "Product") is a non-opioid, non-NSAID analgesic that is a potent and selective cholinergic channel modulator. It is expected to have no tolerance, dependence or abuse potential and no DEA scheduling. ABT-594 is orally-administered, and BID dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain.

The IND filing of ABT-594 was in 1Q1998. A Phase IIb (dose ranging) trial will begin April 2000 in neuropathic pain. A Go/No Go decision for clinical efficacy is expected February 2001. The NDA filing is expected in 2Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release). Total world wide peak sales of ABT-594 are projected to reach over $800MM by 2009.

The US Market of Neuropathic Pain

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. The economic burden of pain in the United States is estimated at $100 billion a year in direct and indirect costs. Approximately 95 MM Americans per year receive drug therapy for pain, which represents about 50% of those who suffer from pain.

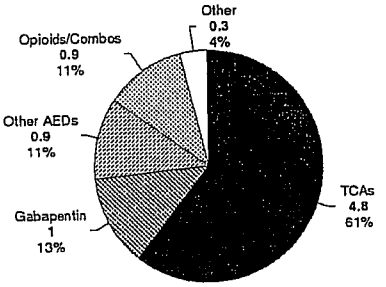
Despite its prevalence, pain is often inadequately managed. There have been few major advances in pain therapy over the last several decades, and pain management continues to rely on nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids and certain adjuvant analgesics.

In the last five to ten years, advances in neurobiology and the development of more sophisticated animal models of clinical pain have led to a paradigm shift in the understanding of pain mechanisms. Not all pain states are the same, and different mechanisms may contribute to pain caused by non-injurious stimuli (acute nociceptive pain), by tissue injury (inflammatory pain) and by nerve injury (neuropathic pain). Tissue and nerve injury induce changes in pain pathways in the nervous system, resulting in altered processing of noxious and non-noxious sensory information, and reveal molecular targets which may not be involved in the processing of sensory information from healthy tissue.

Neuropathic pain is a very large, yet largely untapped market. Estimates vary widely for the number of worldwide sufferers, from as low as 20 million to as high as 50 million or more. The number of actual cases is difficult to estimate since neuropathic pain is difficult to diagnose, and is often misdiagnosed.

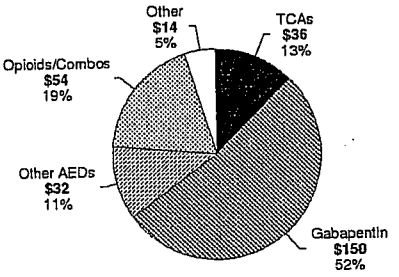
Neuropathic pain is often treated with adjuvant analgesics such as tricyclic antidepressants, anticonvulsants and alpha adrenergic agonists. In the U.S. alone, approximately $200 million of the sales of the anticonvulsant Neurontin (gabapentin) are off label uses attributed to the treatment of neuropathic pain. However, a significant unmet need exists in the treatment of neuropathic pain since few medications provide complete pain relief and most adjuvant medications have significant side effects that preclude their long-term use. As more effective and tolerable medications become available, the neuropathic pain market is expected to experience significant growth.

U.S. Neuropathic TRx (MM)



1998 Neuropathic Pain TRx = 8 MM

U.S. Neuropathic TRx Sales ($MM)



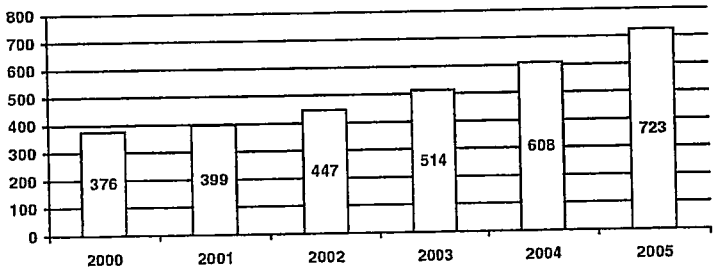
1998 Neuropathic Pain TRx Sales = $286 MM

Sources: IMS Audits and Decision Resources 9/99 Neuropathic Pain Report

US Market Projections

The US neuropathic pain market is expected to grow at a double digit, as a result of the introduction of new therapies (e.g. pregabalin in 2001) , the continued increase in physicians' awareness of anti-convulsants' utility as analgesics, and the expansion in the prevalent population. The market is projected to reach over $700MM in 2005.

US market forecast ($MM)



Sources: Abbott analysis

Scientific Rationale for ABT-594

Recent findings in the understanding of pain mechanisms have led to a new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability. A significant unmet need exists in the pain management market for products that are safer, non-abusable, non-addicting, non-scheduled, non-tolerance producing, and efficacious in oral and parenteral forms for the treatment of moderate to severe pain, especially for chronic nociceptive and neuropathic pain.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. The preclinical side-effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective cholinergic channel modulator (ChCM) with high oral bioavailability in rat, dog, and monkey.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first cholinergic channel modulator to receive an indication for pain. It has a novel mechanism of action, a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having a equivalent/superior efficacy to other drugs used to treat neuropathic pain.

Clinical Studies

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous systems to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro,* at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximally tolerated dose. In subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule(HGC) suggest that higher doses would be tolerated. A phase IIa study with ABT-594 SEC formulation suggests a trend towards analgesic effect at 75ug BID. ABT-594 is generally well tolerated in the dose range. Adverse events include dizziness, nausea, vomiting, asthenia, and diarrhea, all of which were considered mild by investigators.

Phase IIb study for neuropathic pain will begin in April, 2000 and ends in November, 2000. 320 patients will be included in the study.

Patent Status

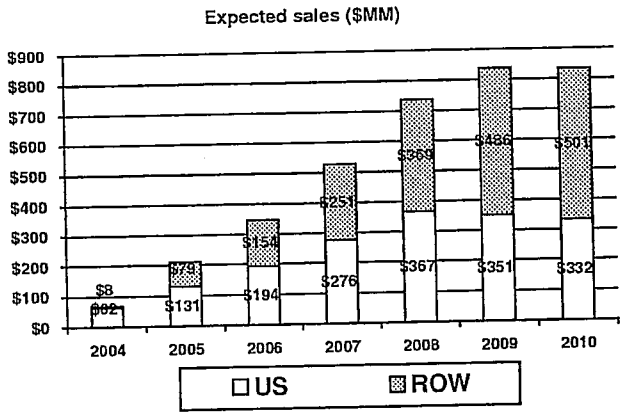
A patent has been granted from the United States Patent and Trademark Office on an application providing generic coverage for ABT-594 and a large class of structurally related analogs. The original filing date for

this application dates back to October 9, 1992. The expiration of patent coverage for composition of matter for ABT-594 will be June, 2016.

An additional application (6013.US.01), which includes species claims to ABT-594 as well as use claims for the treatment of pain, was filed in December, 1996 and is pending. If this patent is allowed, it will provide 20 years from date of filing, which will extend the patent life of ABT-594 and ABT-259 to December, 2016.

The original application providing generic composition of matter coverage was filed broadly ex. U.S. (WO94/08992) and this application published on April 28, 1994. A second foreign filing (WO96/40682) published on December 19, 1996. These cases are all still pending.

Financial Projections



Assumptions for Financial Projections

- Base Case assumes Neuropathic Pain claim and published study in Chronic Nociceptive Pain
- Filed 5/03, Launched 5/04
- MD targets 20% FP/GP/IM, 50% Neuro, 25% Rheum
- Price based on Ultram, '98 AWP $2.72/day, increases 2%/year
- Peak Share 10% for Persistent Chronic Pain, 20% for NP, both in Yr 5

Appendix 1

Key BPH Products in Development – Phase II and Higher

Product	Company	US Dev Phase	Class/MOA	Comments
pregabalin	Parke-Davis	III	Ca channel alpha2delta	Also for epilepsy, chronic pain
GV 196771	Glaxo	II	glycine antagonist	Neuropathic pain & chronic pain
memantine	Merz	II	NMDA antagonist	Dose ranging trial with 375 patients now underway
PN 401	ProNeuron	II	Unknown	For disease modification of PDN - pain & numbness next
prosaptide	Myelos	II	Unknown	14 amino acid peptide Pain associated with nerve injury
resiniferatoxin	Afferon	II	vanilloid	Topical capsaicin analog
LTA	Astra	II	sodium channel blocker	Topical w/ longer duration of action than capsaicin
CNS 5161	Cambridge Neuroscience	I	NMDA antagonist	Will not move to Ph II until a development partner is found

PLs' CE

June 2000
ABT-594 Project Status Report

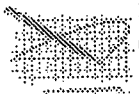
Monthly Highlights

- Experimental placebo manufacturing run prepared at PPD's Puerto Rico Manufacturing Plant (AHPI) in the Potent Drug Module. Special thanks to Serafin Torres and the API plant personnel, and PARD team members Rhonda Peck, Erskine Hilyer and Ji Zhou for their commitment and long hours!
- Enrollment in M99-114 is slower than planned and is under scrutiny by team personnel. (See July Progress Gauges below.)

Key Progress Gauges - June Accomplishments	Target Date	Status
• Begin testing for release and stability initiation of the 3 NDA lots of drug substance	6/5	Incomplete – Delay due to specification system issues (see below) Revised Target: 7/21
• Issue new drug substance test document	6/5	Incomplete – Delay due to issues surrounding new specification documentation system. Revised Target: 7/21
• Complete Development Plan preparation meetings	6/16	Complete
• 90 patients enrolled M99-114	6/25	Incomplete – 73 enrolled as of 6/30
• 2/3 of sites actively enrolling patients M99-114	6/25	Incomplete – 18 / 29 sites actively enrolling, 24 / 29 sites actively screening
• Obtain validated results for ICH Category 1 solvent DCE in 594 clinical drug substance lots and starting material	6/25	In Process
• Discovery Project Team to identify 3 potential follow-on compounds for advanced preclinical characterization	6/30	Complete
• Develop cholinergic channel modulator scientific franchise strategy	6/30	Complete
• Complete preparation for experimental capsule manufacturing run at AHPI (8/00) to assess environmental/employee exposure	6/30	Complete

July Projections	Target Date	Status
• Contact all M99-114 investigators to determine enrollment obstacles	7/5	
• Review early terminations and Adverse Event profile to determine strategic options to address slow enrollment	7/12	
• Finalize recommendations and initiate recommended strategies	7/21	
• Issue new drug substance test document	7/21	
• Begin testing for release and stability initiation of the 3 NDA lots of drug substance	7/21	
• 90 patients enrolled M99-114	7/31	
• Schedule active capsule experimental manufacturing run at AHPI for 8/00	7/31	

PLs' CF



Marilyn J Collicott
06/09/2000 01:21 PM

To: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT
cc: Carol J Feige/LAKE/PPRD/ABBOTT@ABBOTT, Joan M Perri/LAKE/PPRD/ABBOTT
Subject: Updates for M99-114 Phase IIb Meeting

Bruce

Here are my most recent updates for the Phase IIb meeting on Monday. Carol or Joan should be able to update you with any additional randomizations/early terms that occur on Monday.


Earlyterms.doc Investigator tracking.x

M99-114 Premature Terminations

Investigator	Pt. Number	Age	# Doses	Reason for Termination	Comments
Baumel	4145	85	2	AE	nausea, etc.
Bromberg	4113	69	20	AE	nausea, etc.
Bromberg	4115	45	10	AE	nausea, etc.
DeBold	4051	71	18	AE	nausea, etc.
Drucker	4001	72	7	AE	joint pain in lower extremities
Drucker	4002	71	6	**SAE**	palpitations
Drucker	4003	78	1	AE	blurry vision
Eisner	4241	80	1 or 2	AE	nausea, etc. (went to ER)
Eisner	4147	85	22	AE	dizziness, weakness, sweating, blurred vision, heartburn, headache
Fried	4083	66	28	**SAE**	syncopal episode related to historical atrial fib (admitted to hospital 5/30)
Holmlund	4193	53	15	AE	vomiting,, sleepiness
Kipnes	4065	64	7	AE	nausea
Kluge	4131	70	17	AE	nausea, etc.
Sivakumar	4036	59	7	AE	nausea, etc.
Storey	4098	70	13	AE	nausea, etc.
Storey	4100	56		AE	nightmares
Weinstein	4018	68		Withdrew Consent	

PLs' CI

sblewitt@jhancock.com
07/07/2000 04:23 PM

To: Steve Cohen/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Questions

Steve,

In advance of our call on Monday, for each of the products, I would like to walk through the following information:

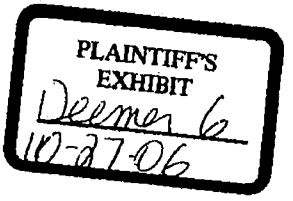
Current status of clinical trials (i.e., what is current stage, what were results from prior stage or interim results -- specifically, trial design and endpoints, discussions with FDA, Go/NoGo decision points). Potential labeling issues. Potential manufacturing issues. Timeline for completion of trials, NDA filing, Approval.

Commercialization rights and freedom to operate.

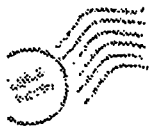
Patent status.

Thanks,

Steve.



PLs' CJ



Bruce McCarthy /LAKE/PPRD/ABBOTT

07/07/2000 11:13 AM

To David D Morris/LAKE/PPRD/ABBOTT@ABBOTT, James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Andrea Landsberg/LAKE/PPD/ABBOTT@ABBOTT, Michael K Biarnesen/LAKE/PPRD/ABBOTT@ABBOTT, Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT

cc Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject M99-114 Protocol Change Discussion

I've scheduled a meeting next week to discuss options to modify the 114 protocol. Enrollment has not met initial expectations. At the present rate of enrollment, data would not be available until June or July of 2001. We in the venture continue to work to address this situation by reasonable encouragement to sites and other modifications to the management of the study (including removal of poorly enrolling sites and replacement with back-up sites). Several protocol-related issues, however, may outweigh any encouragement or management strategies.

Of the 78 subjects enrolled to date, at least 31 have pretermed. Of those, at least 20 appear to have pretermed for AEs typical of our drug (nausea, vomiting and/or dizziness). Although three of these subjects dropped on day one (when they would have, at most, been exposed to 75 mcg), many of these subjects dropped in the 3-11 day time frame (the period of dose escalation resulting in 150 mcg BID at day 4, 225 mcg BID at day 6 and 300 mcg BID at day 8). Appropriately, the preterm rate has created investigator and coordinator reluctance to enroll (or, more particularly, individual sites' experience with preterms). One option to address this concern would be to remove the top dose(300 mcg BID). This doesn't address all of the issues, in that we continue to be blinded and don't know how many of these subjects that dropped out would have been randomized to 150 or 225 (assuming all events are drug related). We would, however, be responding appropriately to sites' concerns and may reduce their appropriate concerns about enrolling subjects because subjects would no longer risk randomization to the 300 mcg dose.

In addition, as with the prior study (833), there continues to be significant investigator and coordinator head-wind related to a study design that requires subjects to be off all analgesics. One option is to remove this requirement and allow subjects to enter the trial on some level of concomitant analgesia.

Please consider the ramifications of these and other possible protocol design changes in preparation for this meeting. Let's begin to discuss these possibilities for implementation in the next few weeks. The optimal enrollment time extends until 9/22/00 (in terms of date of randomization)-after that, subjects starting on drug would be in the study during the holiday season and enrollment is likely to decrease. Any changes should be incorporated into a protocol amendment to be signed off the week of7/17 so that they can be distributed for IRB approval. That timeline might allow a majority (and I mean 50%) of sites to be able to implement the changes by mid August.

Thomas DEP. EX. NO. 7

FOR ID., AS OF 4/13/07

CONFIDENTIAL
ABBT0082516

PLs' CK

Michael K Biarnesen
07/25/2000 09:14 AM

To: Aldona T Matalonis/LAKE/PPRD/ABBOTT@ABBOTT
cc: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT, Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Re: RQA auditor assignment for Analgesia Venture

For ABS and NPS, Cheryl indicated that Teresita and Mickie should be invited. I'll follow-up with Cheryl and Belinda for clarification on all our activities.

Mike B
Aldona T Matalonis

Aldona T Matalonis 07/25/2000 08:03

To: Michael K Biarnesen/LAKE/PPRD/ABBOTT@ABBOTT, Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT
cc: Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT
Subject: RQA auditor assignment for Analgesia Venture

FYI:
It's not clear to me if Teresita is our RQA contact for *all* Analgesia Venture compounds/projects. I will pursue any potential 114 drug supply issues with her:

Mike- Did you get an answer from Cheryl Spencer or Belinda regarding who will be assigned to 089,1776,103 and/or vicoprofen efforts?

Aldona

---------- Forwarded by Aldona T Matalonis/LAKE/PPRD/ABBOTT on 07/25/2000 08:58 AM

From: Susan M Powers on 07/24/2000 02:42 PM
To: Aldona T Matalonis/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: RQA concerns for potential changes in M99-114 randomization assignment via IVRS

Aldona,
Teresita Curry has been assigned to be the auditor for the Analgesia Venture I forwarded your earlier message to Tita and Mickie, but thought that it would be a good idea to inform you of the venture assignment change.
Kind regards,
Susan

---------- Forwarded by Susan M Powers/LAKE/PPRD/ABBOTT on 07/24/2000 02:40 PM ----------

From: Susan M Powers on 07/10/2000 09:18 AM
To: Mickie Radjenovich/LAKE/PPRD/ABBOTT@ABBOTT, Teresita P Curry/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: RQA concerns for potential changes in M99-114 randomization assignment via IVRS

---------- Forwarded by Susan M Powers/LAKE/PPRD/ABBOTT on 07/10/2000 09:17 AM ----------

Aldona T Matalonis 07/07/2000 08:35

To: Susan M Powers/LAKE/PPRD/ABBOTT@ABBOTT

cc: Belinda A Hightower/LAKE/PPRD/ABBOTT@ABBOTT, Julie V Jervis/LAKE/PPRD/ABBOTT@ABBOTT, Tamara L Garavalia/LAKE/PPRD/ABBOTT@ABBOTT, Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT
Subject RQA concerns for potential changes in M99-114 randomization assignment via IVRS

Susan-
We would like to discuss any potential RQA concerns regarding study drug distribution(via IVRS) and site drug accountability for the following *potential* scenario:
The Analgesia Venture *may* be changing the double-blind study drug assignment arms for ABT-594 study M99-114 from:

1:1:1:1
Placebo
ABT-594 300mcg BID
ABT-594 225mcg BID
ABT-594 150mcg BID

to

1:1:1
Placebo
ABT-594 225mcg BID
ABT-594 150mcg BID

The study currently has 79 subjects randomized to the original four arm protocol.
There is some concern with what *may* be AE's due to the higher 300mcg dose and also other study design elements.

(Further discussion between STATS, Regulatory and the Venture will commence next week to review major 'big picture' concerns.)

Our plan to accomplish this change in study drug assignment and distribution via the ClinPhone IVRS drug distribution system can be smoothly accomplished with their validated databases and would not require extensive handling of drug supplies at the site. ClinPhone would simply *not* assign any 300mcg modules of drug, once the study design is officially approved.

The documentation and logistics at the site will need to be clarifiied.
I will call you next week to discuss specifics.
Thanks very much,
Aldona

PLs' CM

ABT-594 Product Development Team Meeting

Tuesday, August 1, 2000
1:00pm - 2:30pm
AP30-3E-Cafeteria

Minutes

Attendees:

Mike Biarnesen, Bruce McCarthy, Chris Silber, Michael Meyer, Jim Thomas, Julia Hui, Aldona Matalonis, Barbara Massa, Andrea Landsberg, Laura Robinson, Lloyd Dias, Marilyn Collicott, Michael Branton, Ji Zhou, Joe Machinist, David Ross, Yiming Zhang, Tamara Garavalia, Carol Feige, Phyllis Christensen, Joan Perri, Beth Wilson, Susana Dennis, Walid Awni, Rhonda Peck, Sandeep Dutta, Tawakol El-Shourbagy, Russ Slade, Howard Cheskin, Xavier Frapaise, Cathy Kacos.

Agenda:

Mitsunobu (Dave Stroz):

Japan Registration Requirements:

Commercial Capsule (Mike Biarnesen):

[insert slide]

We will also need to think about capsule bottle size (number of capsules in a bottle).

Puerto Rico Manufacturing (Lloyd Dias):

A safety run was conducted this month and most everything went well. There were some minor issues that need to be addressed. This was not a formulation run. A report will be ready in a couple of weeks.

There are some ideas for a scale-up and activities, scheduled for early 2001.

Development Plan:

Silber DEP. EX. NO. 1 14
FOR ID., AS OF 2-9-07 BC

Many thanks went out to those individuals who have put in much time and effort in the draft Development Plan. A new draft went out last week for further evaluation and edits. Comments were due on Monday, August 28th, however, we are still waiting for feedback from some individuals. The deadline for final completion of the Development Plan was originally scheduled for August 31st, but an extension was granted to September 30th.

Area Updates:

Study M99-114 (Marilyn Collicott)
Currently we have 135 subjects randomized with an approximate 51% screen failure rate and a 30% drop-out rate. Our goal of enrollment is 320 subjects. There has been an increase in activity lately, probably because the Principal Investigators know we are nearing the end of the enrollment period (there were 12 subjects screened on Monday and Tuesday). We are planning on dropping the sites that have not randomized any subjects, which will bring our number of sites down to 28 from 31. Our newest Investigator is Dr. Aziz Shaibani from an SMO (West Pharmaceutical Services). Dr. Shaibani has already screened 3 patients on Monday.

A survey was sent out to sites to examine AEs (nausea, vomiting, and dizziness). Demographic characteristics were also observed (subject weight was predominant).

We are currently looking into the possibility of extending the enrollment period (enrollment planned to end on September 22, 2000).

Study M99-115 (Marilyn Collicott)
The osteoarthritis study has been funded. There is a possibility of starting the study this year. All sites have approval.

Study Drug Supplies (Aldona Matalonis)
We will still have enough study drug, even if enrollment is extended for the M99-114 study. For the M99-115 study, partial blistering has been completed and everything was left "on hold." We will need to let IDS and production know when we have a "go" on the study. We will also need to start discussions on Phase 3 supplies.

We will need to know as soon as possible if an active control vs. placebo control study will be required (compared to Gabapentin). Comparator trials may be required ex-U.S. as pivotal trials.

Data Management (Beth Wilson)
Thanks go out to the Clinical team for being patient as Data Management used M99-114 to pilot the new QA Plan. The first queries have now been printed and sent. CDM is ready to make a quick start with the M99-115 CRFs as soon as they get the go ahead.
Statistics (Jim Thomas)

No new updates to report.

Drug Analysis (Tawakol El-Shourbagy)
No new updates to report

Pharmacokinetics (Sandeep Dutta)
No new updates to report

Regulatory (David Ross)
Regulatory received a call from the FDA. The FDA review division has been changed for our study drug. We are now reviewed by the "Critical Care" division, whereas our drug was formally reviewed by the "Drugs with Abuse" division. Historically, the Critical Care division reviewed NSAIDs. We will need to file a new IND. We already have an IND in place from our Molar Extraction study.

Regulatory has also been working with Commerical (Andrea Landsberg) on a USAN name. Three names were selected and the top selection was "ebanicline tosylate." Ironically, this is also a name that USAN selected.

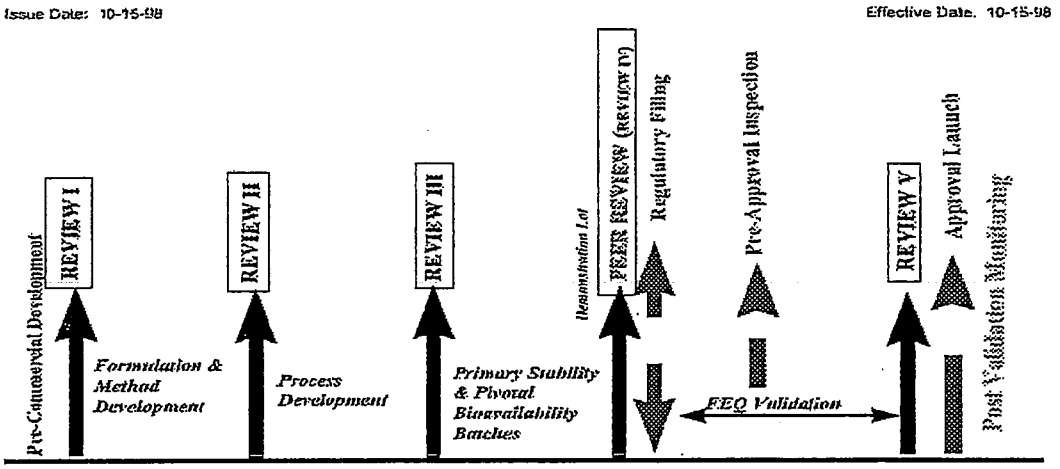
Commerical (Andrea Landsberg and Laura Robinson)
An internal professional design department has been hired to design a global look for our capsule. They expect to have something by the end of October. Commercial is also still working with our trade name.

PARD (Howard Cheskin)

Review II: Formulation/Process and Methods Development

Stage of Development:
- Phase II/proposed Phase III
- Identification of dose strengths and proposed formula/process
- CAPD and PPD process at pilot plant scale
- Planned CAPD qualification and PPD production scale process runs

Key Risks: Relative to impact on development
- Bulk substance issues:
  - Final synthetic route identified and suitable for proceeding to the next scale
  - Cost v. quantities needed
  - Bulk substance sourcing plan
  - Safety and Handling requirements
- Formulation/Process issues:
  - Formulation/ process studies support proceeding to the next scale
  - Drug product sourcing plan
  - Safety & Handling and Cleaning requirements updated



Attachment 1. Commercial Product Development Continuum

A Commercial Product Development Continuum Review will be held for ABT-594. Peer review will be Oct 2 and management review will be Oct 20. Continuum reviews serve as CMC status reviews and risk assessments throughout the development cycle of commercial products.

Drug Safety (Julia Hui)

The male mid-dosage group in the rat carcinogenicity study was terminated on 8/29/00 due to dropping of the group's survival number to 20. All other groups for the study are still ongoing. The scheduled necropsy for this study starts on 9/14/00.

The mouse carcinogenicity study is still ongoing with good survival.

Biotransformation/Human Metabolism (Joe Machinist)
The Biotransformation/Human Metabolism team is currently writing the human radio-labeled study protocol. The study will be at Covance on October 19th. We will need to fund 2 future human metabolism studies (at Inveresk).

Discovery (Mike Meyer)
The Discovery team continues to target a December DDC date for a backup compound to ABT-594. A-312046 is currently the best lead, and it is believed that this compound fulfills the safety and efficacy criteria for a follow-on to ABT-594. However, recent results from pharmacokinetic evaluation in dog and monkey have raised issues for this compound. Although the oral bioavailability and plasma half life of A-312046 in the rat are at least equivalent to ABT-594 (80% oral bioavailability) and perhaps superior (2-fold longer half life), bioavailability in the monkey is clearly inferior (3% oral bioavailability vs. 80% for ABT-594). Bioavailability in the dog for both compounds is relatively poor. The project team is currently evaluating absorption and metabolism across several species using in vitro models to determine whether A-312046 may be predicted to have an acceptable pharmacokinetic profile in man. In addition, several structurally related compounds with comparable efficacy and safety profiles (A-348833, A-343011, A-350779) are currently undergoing evaluation in the rat, dog, and monkey to determine whether the poor bioavailability in the monkey is compound specific or a general phenomenon for this chemical series.

Concurrently, the project team is evaluating a series of compounds that exhibit good efficacy in models of inflammatory pain, but poor efficacy in models of neuropathic pain. The best candidate compound with this profile (A-333094) is currently undergoing more complete evaluation in models of efficacy, safety, and pharmacokinetics.

Finance (Barbara Massa)
The 2001 budget should be final by today. If there are any additions or changes, individuals should notify their financial analyst.

PLs' CN

ABT-594 Product Development Team Meeting

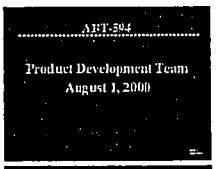
Tuesday, August 1, 2000
1:00pm - 2:30pm
AP30-3E-Cafeteria

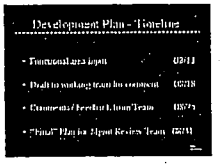
Minutes

Attendees:

Mike Biarnesen, Bruce McCarthy, Chris Silber, Jim Ciullo, Michael Meyer, Jim Thomas, Julia Hui, Aldona Matalonis, Barbara Massa, Stan Roberts, Andrea Landsberg, Laura Robinson, Dave Stroz, Lloyd Dias, Marilyn Collicott, Teresita Curry, Dianna Ambrose, Michael Branton, Ji Zhou, Joe Machinist, Cathy Kacos.

Agenda:





2001 Plan Update:

Currently, we have $35 MM funded for 2001, which includes the osteoarthritis study. However, we will try to have the OA study moved to this year. This also includes Phase III studies on neuropathic pain, assuming a "Go" decision.

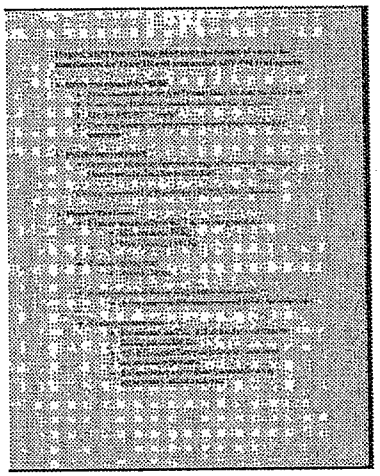
Leiden EXHIBIT 9
FOR I.D. 4-26-07 /

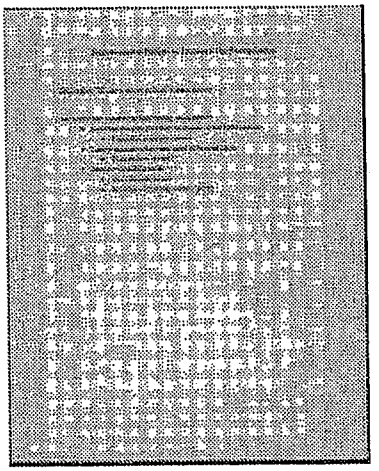
2001 Studies:

Several Phase I, Phase II, Phase IIb and Phase III studies have been proposed for 2001. Among these are an fMRI study and Human Abuse Liability studies. The fMRI study will determine how the brain functions during pain and with pain relief on ABT-594. The fMRI study will be performed by a research group in England.

The Human Abuse Liability study will take 2 stages: 1. Pre-clinical, which will be an independent evaluation of the drug in animal models; and 2. Clinical, which will be performed by Donald Jasinski, MD at Johns Hopkins. There, Dr. Jasinski will enroll drug addicts to compare the addiction of ABT-594 to heroin and cocaine. All new, novel analgesics must go through this type of study.

PARD Update (Lloyd Dias):





The manufacturing site in Puerto Rico is the site of choice in manufacturing ABT-594 capsules. A placebo safety run has been completed. Other than a few very minor problems, the facility appears acceptable from a safety perspective. The highest drug loading will be 1500 mcg/gm.

Capital expenditures for AHPI will be minimal, however, in the long run, the facilities will need to be upgraded. Hypothetically, if AHPI had not passed standards, we do have back-

up sites that are available for manufacturing of ABT-594. However, this would cause a 6-month delay (for testing of new sites).

PARD is also working on a modified formulation to remove the microcrystalline cellulose and to lower the amount of stearic acid.

We currently have enough clinical supplies for the osteoarthritis study this year.

SPD/Analytical Update (Jim Ciullo/Dave Stroz):

DTP (test and spec document for 594 drug substance) issued 7/21/00.

In June, meetings were held to discuss the mesylate route versus Mitsunobu. Both routes include recrystallization and cannot be distinguished. Gopi Menon has indicated that we must look for "remnants" of the process changes as part of the Mitsunobu route assessment. Progress has been limited due to prioritization/resource constraints.

There are NDA lots (3 Chemsyn) under test; all tests to be completed and lots approved by the end of August.

Further chemical investigation for the presence of possible detectable manufacturing impurities of Mitsunobu reaction to be finished 10/31/00. Requires assistance from SPD to synthesize chemical intermediates/reaction mixtures. Also, Mike/Aldona to call cross-functional meeting(s) to determine what is necessary to assess need for Mitsunobu runs at this time. AI Regulatory should be involved in the decision process.

Class I solvents (4 chlorinated + benzene) for the 6 lots of 2-chloro-5-hydroxypyridine and 2 clinical lots of 594 (27-335-YS-00 and 52-015-KD-00), and results to be issued by 8/11. Preliminary readout is that no Class I solvents have been found in any of the 8 samples mentioned.

If we need to make full-scale runs, we will be behind schedule and may not have enough starting materials. However, if we only do partial-scale runs, we will be on schedule with existing starting materials. We will actually plan for 3 full-scale runs for 2001 to determine if the budget can hold that. This will cost approximately $1MM, including head count.

Development Plan (Mike Biarnesen):

We will be sending out sections to certain individuals for their input to the Development Plan. The projected date of completion for the Development Plan is the end of August, 2000. A meeting will need to take place to determine bridging studies in Japan.

Other Updates:

Marilyn Collicott provided an update on the M99-114 (Neuropathic Pain) study. Currently we have 99 subjects randomized with an approximate 50% screen failure rate. Our goal of enrollment is 320 subjects. There has been much concern with the drop out rate. Therefore, we have sent out surveys to each site to determine "who" and "why" subjects are dropping out.

Julia Hui provided an update on the rat carcinogenicity study. We are close to maximum drop out (21 rats). After the study has ended, it will take the pathologist approximately 6 months for evaluations and the report will be ready after that. The FDA has accepted our proposal for managing the drop-out rate. Julia also mentioned that the antigenicity studies will be required for Japan.

Andrea Landsberg updated the name selection for ABT-594. There were several names approved by the Trademark committee. Among these are Numira, Nufora, and Amarquil [check spelling]. Our goal is to have 10 names to bring to market research.

Lloyd Dias mentioned that we will need to start thinking about capsule color. A separate meeting will be scheduled.

Mike Meyer is still looking into back-up compounds for ABT-594. Compound 312046 is similar, along with a few other compounds.

Mike Biarnesen mentioned that, in the future, we may combine the Product Development Team meetings with the Clinical Trial Team meetings to form one monthly meeting.

A separate meeting will be scheduled to discuss the registration requirements for Japan with Nigel Livesey, Laura Robinson, Carol Meyer, Bruce McCarthy, Mike Biarnesen, and Cary Buschen-Schmidt.

PLs' CR

Marilyn J
Collicott /LAKE/PPRD/ABBO
TT

08/31/2000 12:03 PM

To Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT
cc Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject M99-114 Extension letter

Chris -

Here's a copy of the extension letter for your review. Bruce has seen it and his comments have been incorporated.....mc

extension letter.doc

Silber DEP. EX. NO. 17
FOR ID., AS OF 2-9-07 BC

August 31, 2000

<Investigator Name>
<Address>

RE: Protocol M99-114: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy

Dear Dr.:

I am pleased to inform you that the enrollment period for study M99-114 has been extended. The last day for randomization will be March 2, 2001. If we reach our target enrollment before that date the study will be ended at the time when 320 subjects are randomized.

While it may now seem that we have a bit of breathing room, in actuality we don't. The holidays are fast approaching - a time when recruitment and enrollment slows down considerably. We will, in effect, be losing approximately 2 months of our enrollment extension to the holiday season. That will leave us with just 3 ½ months of remaining optimal recruitment time. To put this in perspective, in the last 3 ½ months of this study approximately 110 subjects were randomized. If we enroll the same number during the optimal recruitment period of the enrollment extension, we will have a total enrollment of 240 - 80 subjects short of our goal. These numbers indicate a need to remain focused on recruitment efforts before and after the holiday season.

We expect the holiday season to be challenging in terms of recruitment and enrollment, however, there may be an advantage for many subjects to enroll during this time. If a subject receives pain relief from the study medication, their holidays would be more enjoyable. In addition, subjects should be able to determine whether or not they will tolerate the drug within the first week of therapy. With careful planning of randomization dates, the issue of tolerability is unlikely to interfere with the subjects' holidays.

Please continue to use the upcoming weeks to concentrate your efforts on maximum recruitment and enrollment. Please continue to call us with your enrollment questions. The Analgesia Venture at Abbott Laboratories thanks you for your continuing efforts to make study M99-114 a success.

Sincerely,

Marilyn Collicott
Clinical Project Manager
Analgesia Venture

PLs' CU

Pharmaceuticals Strategy Update

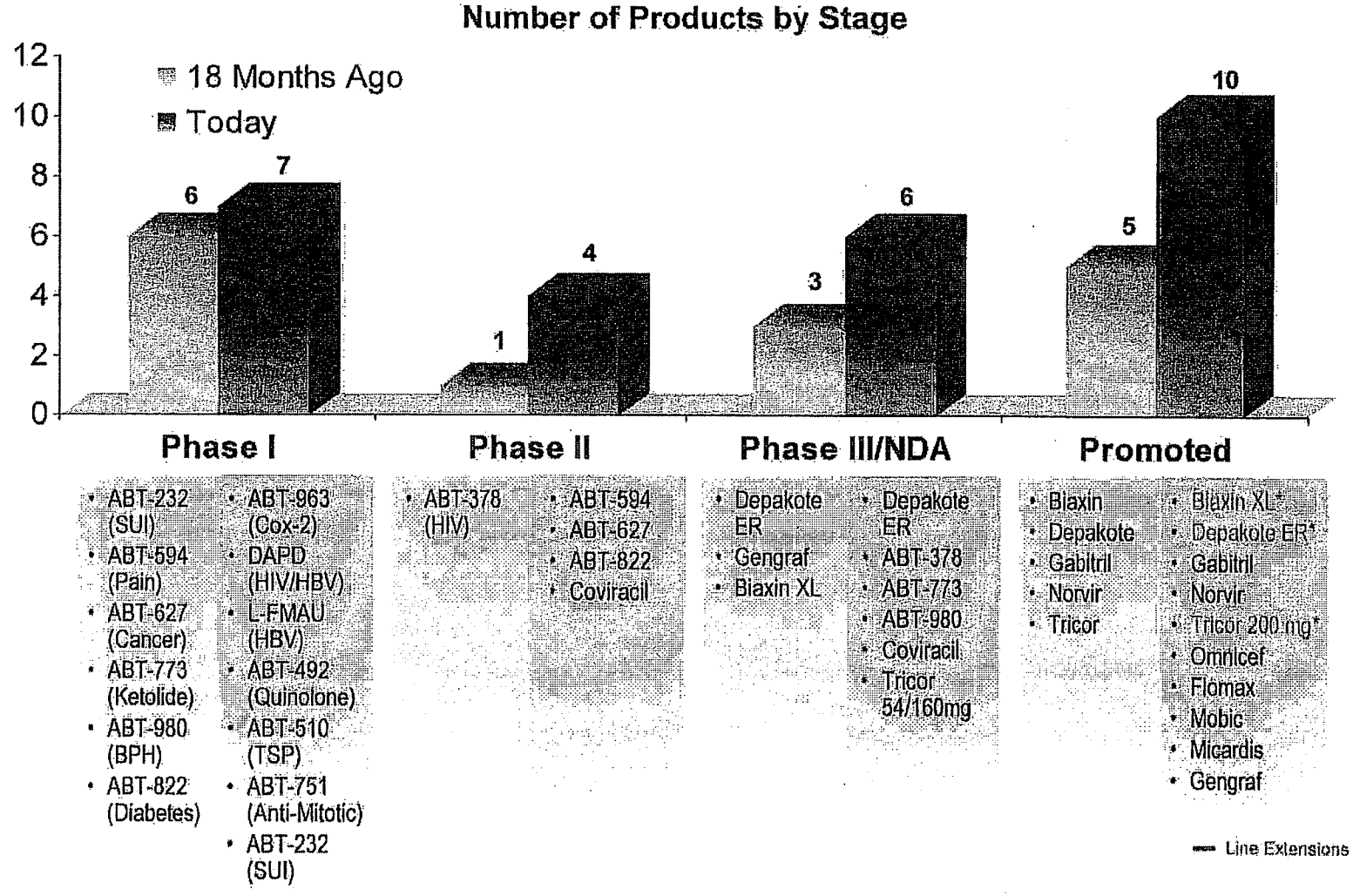
September 2000

For the past 18 months, PPD has been implementing a four-point strategy designed to achieve and sustain double-digit sales growth

- Create stand-alone and P&L responsible businesses, or Franchises, which provide a focused platform for future new products, to improve critical mass in R&D and Marketing
- Re-engineer R&D operations and grow R&D dollars to increase the output of internally-developed new products and line extensions
- Fill the short-term sales gap by accessing new products through an aggressive in-licensing program: focusing on products which broaden existing Franchises
- To sustain long-term growth, pursue strategically attractive acquisitions, with particular focus on biotech and specialty manufacturers

This strategy was first presented to the Board at last year's June meeting in London

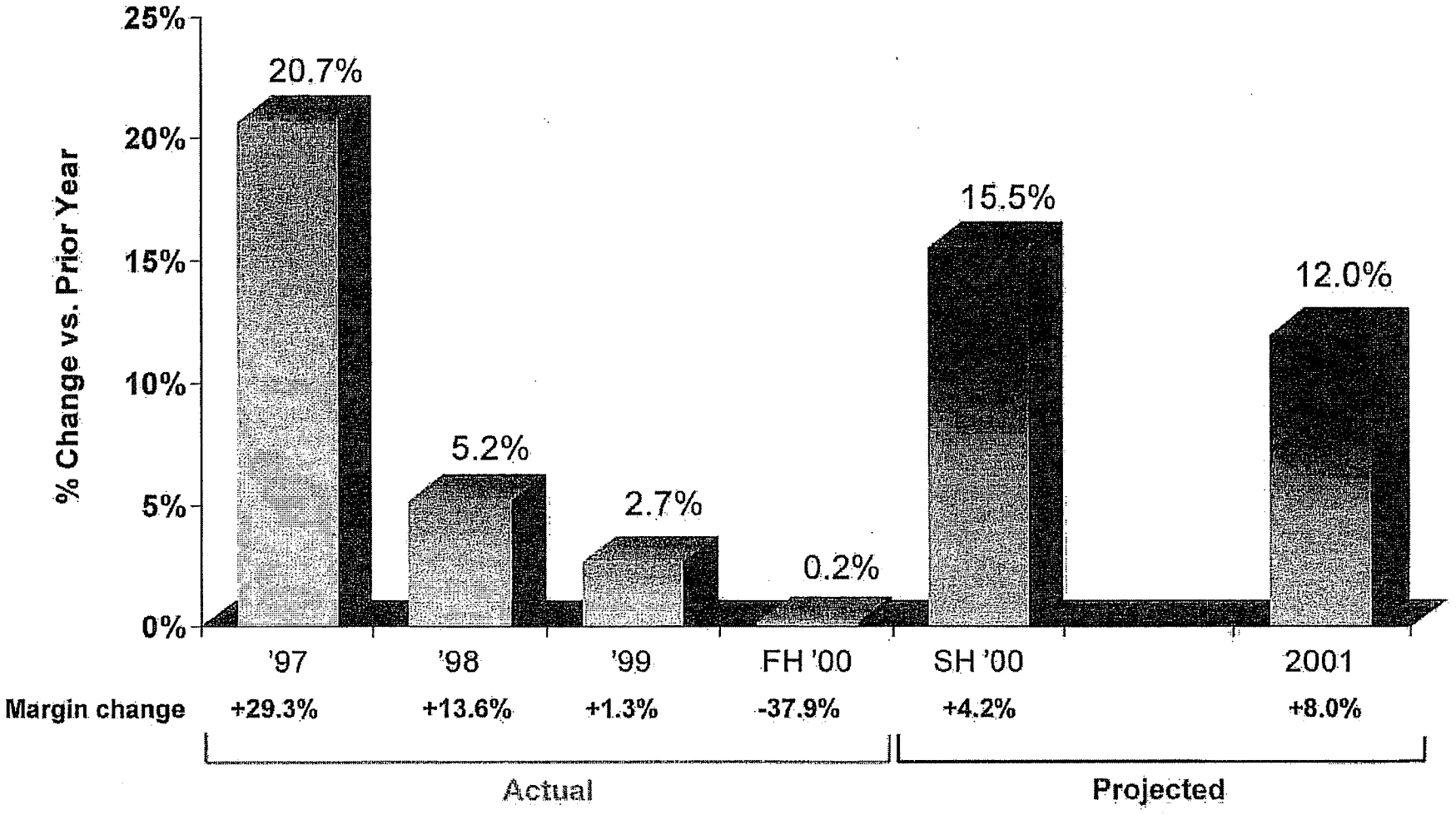
This strategy has focused on increasing the development pipeline through increased productivity programs, spending and external deals



KALETRA, Abbott's new Protease Inhibitor for the treatment of AIDS, is the most exciting of these new compounds

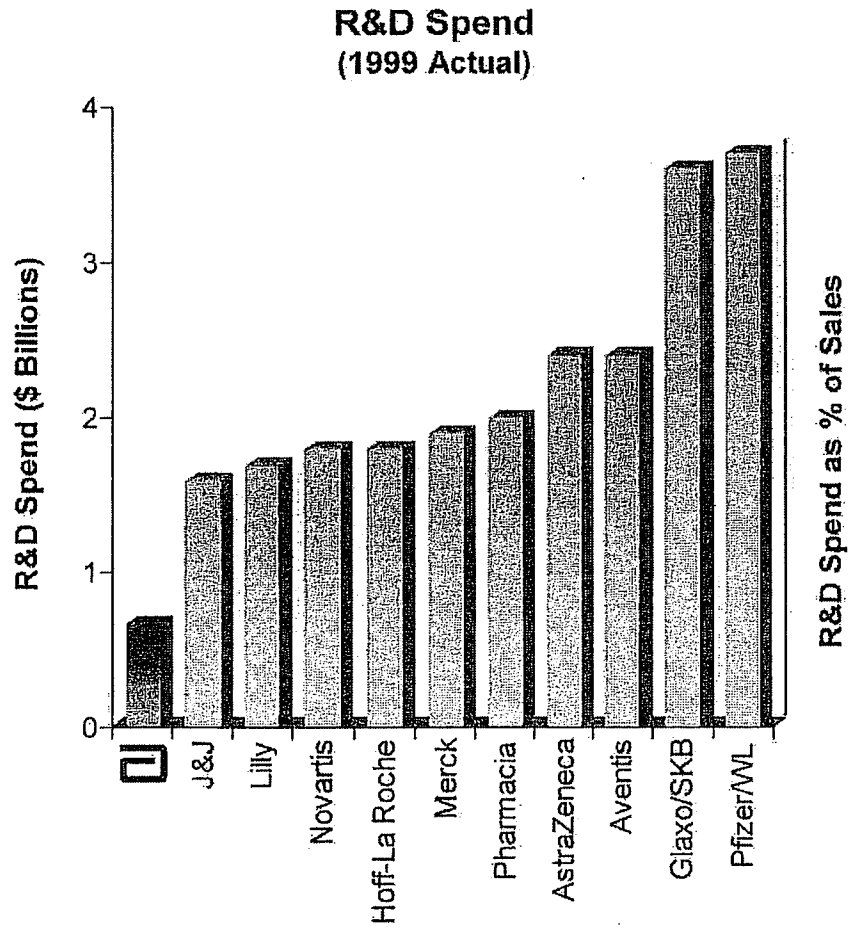
- The goal of the R&D team was to create a "best in class" protease inhibitor. This was achieved with superior efficacy results in place
- Development was accelerated resulting in 46 months from first-in-man to approval, over a year faster than the norm
- Expected approval in the U.S. in August 2000
- Peak year global sales are projected at $600MM

These efforts will result in double-digit sales growth over the next 18 months, but margin growth will be dampened

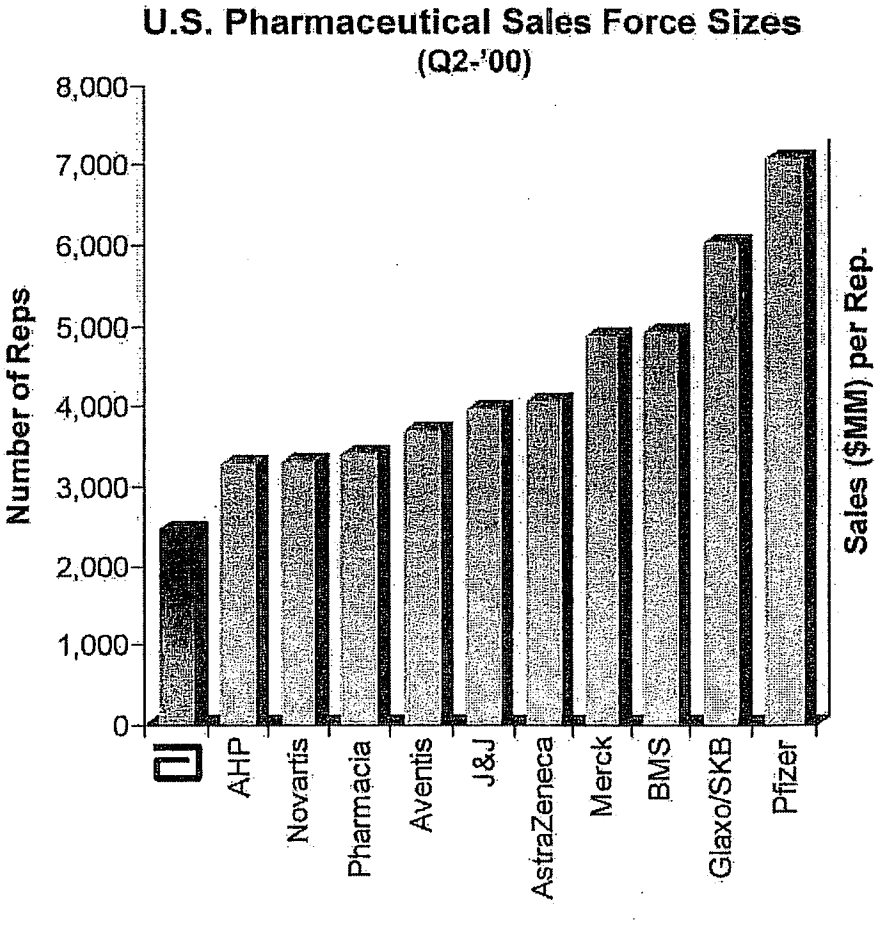


NOTE: Sales figures exclude Abbokinase

These gains were achieved even though Big Pharma continues to use R&D spend and promotional muscle as a barrier to entry. This has served to widen the gap between "big pharma" and the rest of the industry, putting further pressure on profit margins



Source: Wood Mackenzie

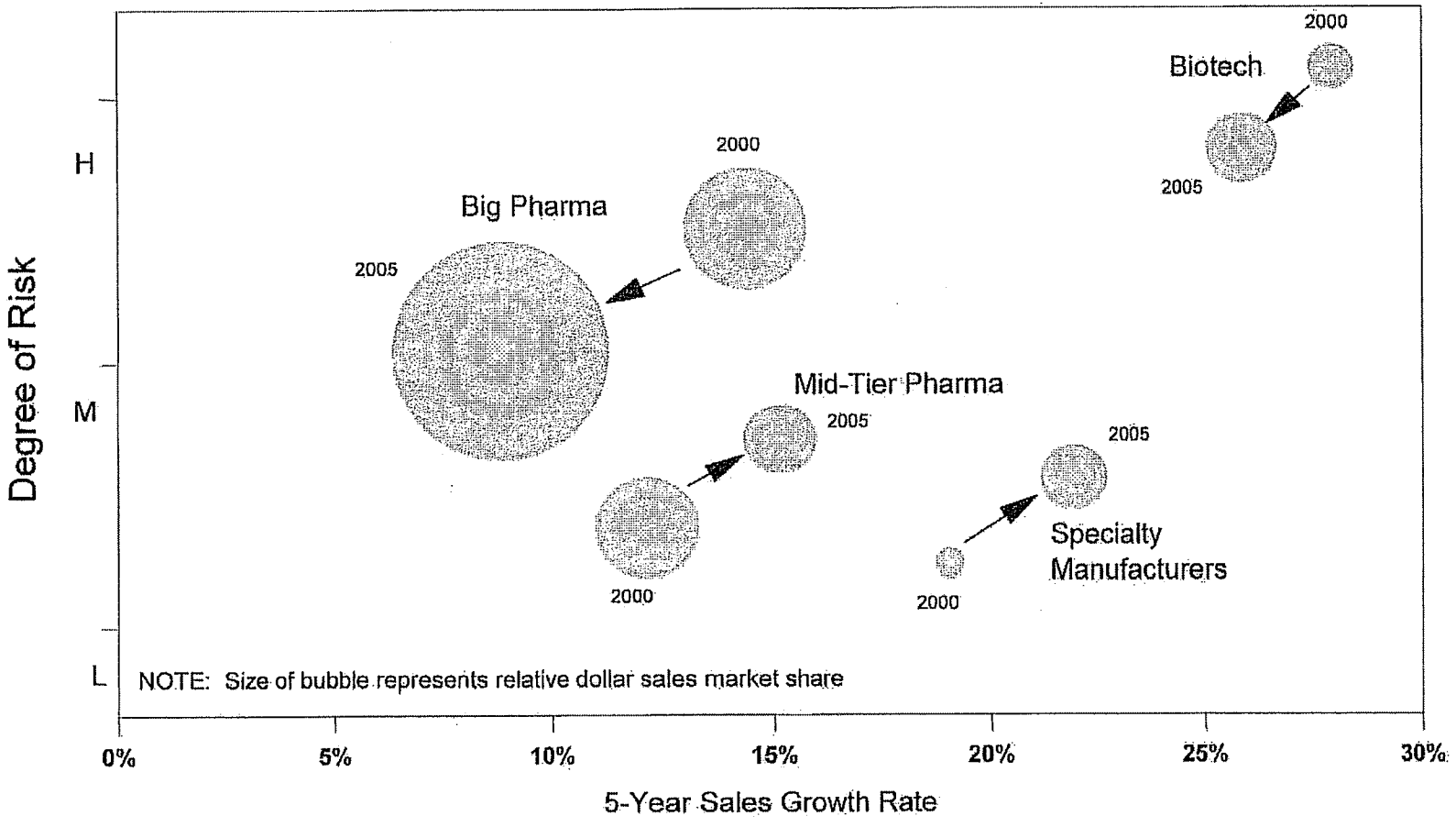


Source: Scott-Levin Salesforce Structures (Q2/00)

Faced with the challenge of R&D and promotional critical mass, the market is separating into four groupings, or business models

- Big Pharma (Pfizer, Glaxo, SKB)
  - Strategy to acquire R&D/sales force critical mass. This has been the industry trend over the last few years. These "mega-companies" must be able to integrate different corporate cultures and introduce several significant NCEs each year to ensure sales growth of 10%+
- Mid-Tier Pharma (Abbott, Schering-Plough, Forest)
  - Strategy to achieve expertise and appropriate scale in specific therapeutic categories. To increase likelihood of success, Discovery is approached through combination of in-house development and in-licensing. Vulnerable to acquisition by larger companies
- Specialty Manufacturer (Alza, Elan, Sepracor)
  - Strategy reduces the product risk by developing improved forms of accepted products. This approach can also shorten time to market but profitability through royalty payments is reduced relative to NCE ownership
- Biotech (Amgen, Biogen)
  - Initially, strategy to partner commercialize assets, progress to narrowly focused, fully integrated companies

These four business models have varying degrees of risk and probability of future sales growth. However, success will be determined by excellence in both R&D and commercialization



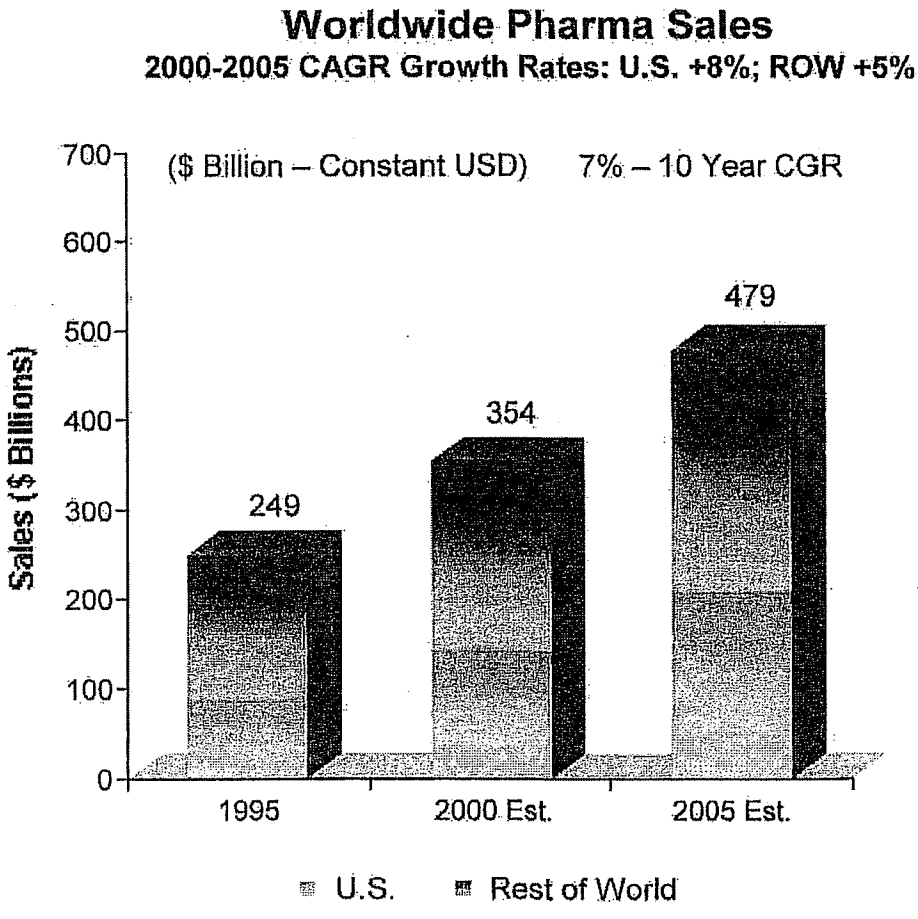
There will be winners and losers in each segment. The losers will be acquired as the industry continues to consolidate

It makes sense to grow the Abbott pharma business from commercial and scientific perspectives

•The pharmaceutical industry is one of the world's largest and most profitable industries. Growth is expected to continue

- Global economic growth
- Aging population
- Acceptance of "lifestyle" drugs

•Recent advances in genomics and molecular genetics will greatly facilitate new drug discovery



Source: IMS Health and Internal PPD Estimates

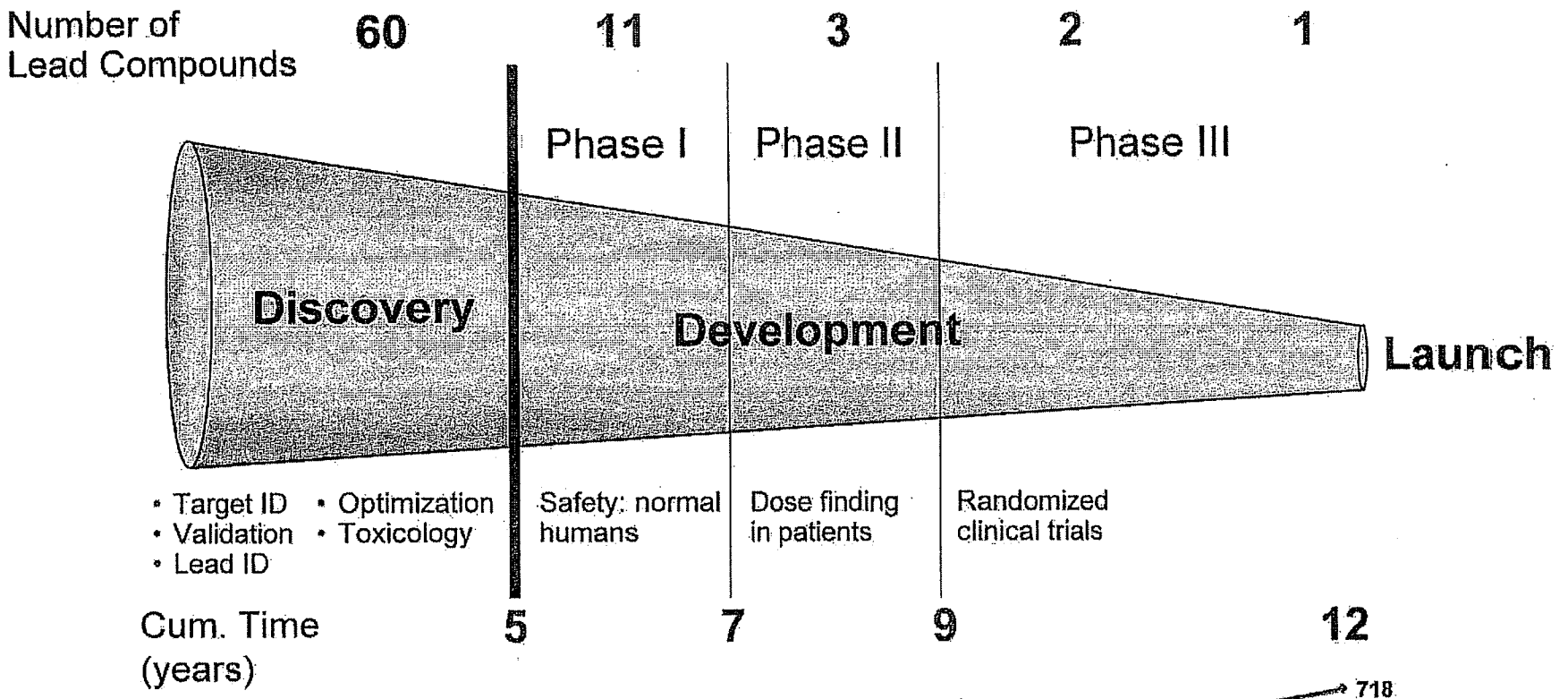
There will be both external and internal challenges to growing the Abbott pharma business

- External Challenges
  - Downward price pressure will continue.
  - Increasingly strict FDA scrutiny process resulting from product recalls (e.g., Rezulin, Propulsid, etc.) will lead to greater R&D costs as well as longer development timelines.
  - Increasingly rigorous regulatory and QA environment will add signficant costs.

There will be both external and internal challenges to growing the Abbott pharma business

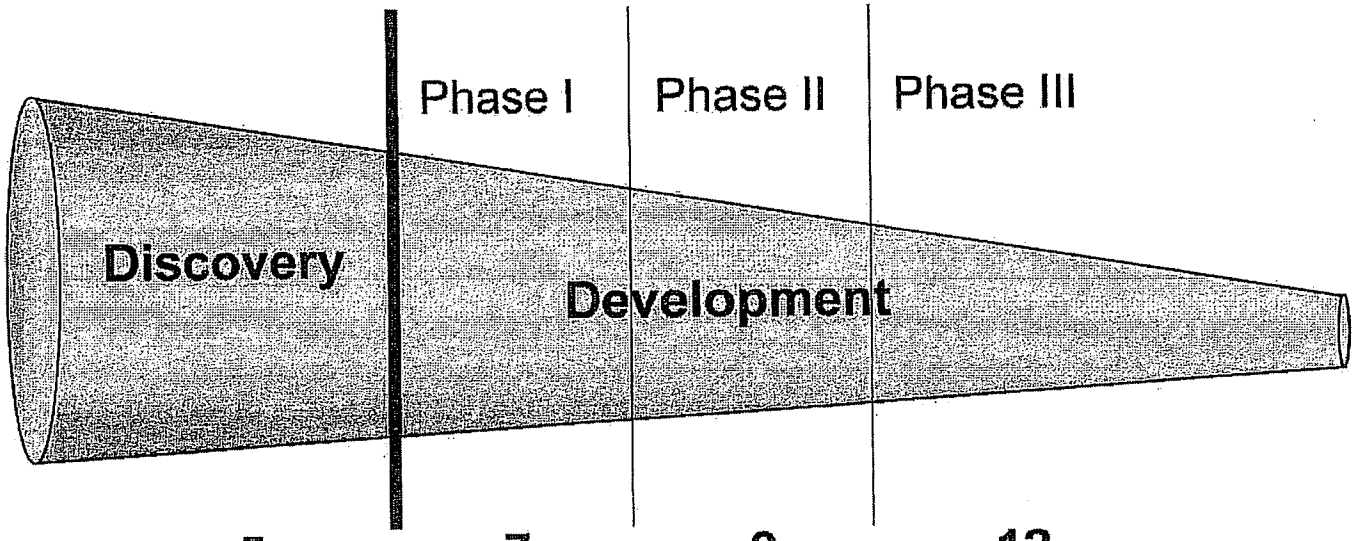
- Internal Challenges
  - The imbalance of our pharma pipeline
    - many early stage compounds; not enough late-stage drugs
  - Affordability
    - We cannot currently afford to develop all of our early stage compounds
  - Fragmented pharma R and D effort
  - Fragmented decision making processes for in licensing compounds

Drug development is a high risk business



Source: Internal data; includes cost of failures

The Imbalance in the Abbott Pipeline



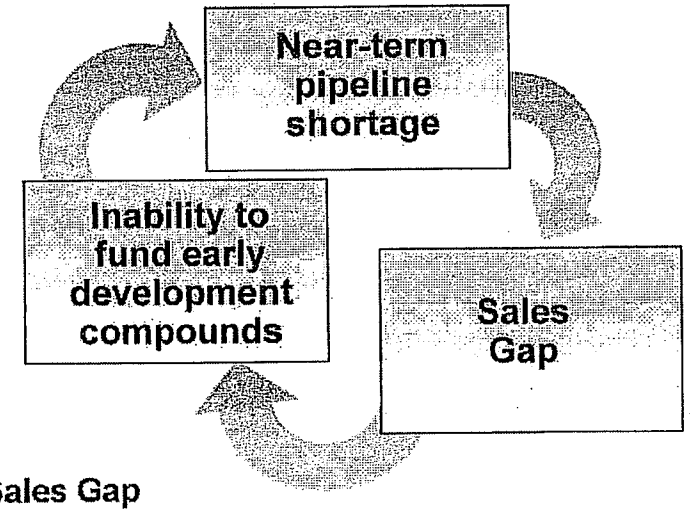
- •Depakote (ER)
- •Biaxin (XL)
- •Prevacid

Cum. Time (years)	5	7	9	12
	• ABT-828 • ABT-598 • ABT-518 • Plus 10 compounds not yet achieving DDC status	• ABT-963 • ABT-492 • ABT-510 • ABT-751	• ABT-594 (pain) • ABT-627 (pr ca) • ABT-822 (DM)	• ABT-378 (HIV) • ABT-773 (Clari repl) • ABT-980 (BPH) • Uprima (ED) • Co-actinon (HIV) • Co-viracil (HIV)

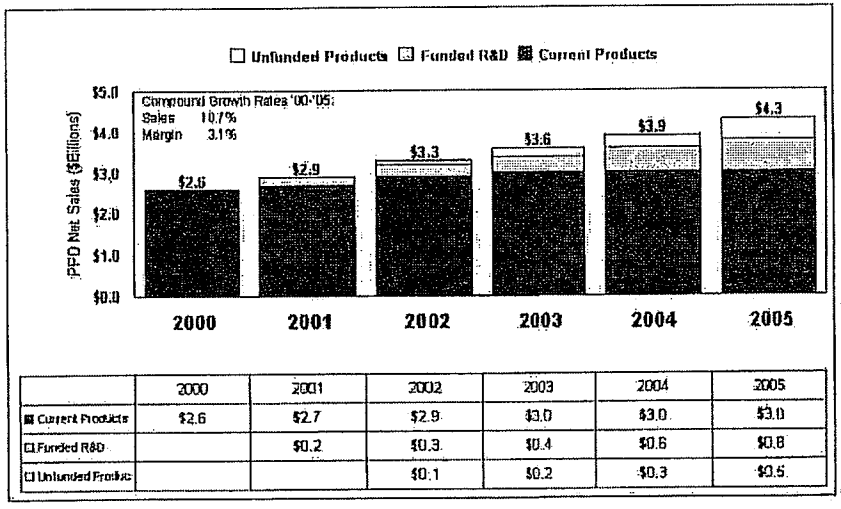
- •Tricor
- •Flomax
- •Omnicef
- •Micardis
- •Norvir
- •Gabitril
- •Mobic

— Significant Commercial Potential (>$500 MM)
— Uncertain Commercial Viability
— Commercially Successful ($250-500 MM)
— Questionable Commercial Viability
— Commercially viable ($100-250MM)

The Near-Term Pipeline Shortage Creates Sales and Funding Problems Over the LRP



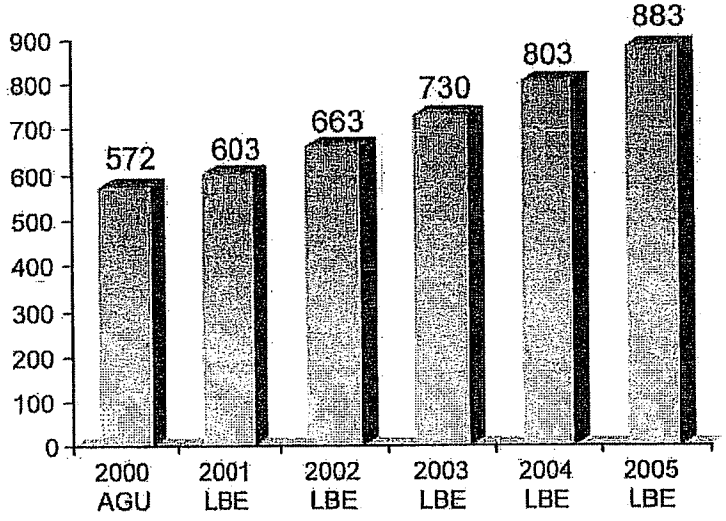
Sales Gap



	2000	2001	2002	2003	2004	2005
Current Products	$2.6	$2.7	$2.9	$3.0	$3.0	$3.0
Funded R&D		$0.2	$0.3	$0.4	$0.6	$0.8
Unfunded Products			$0.1	$0.2	$0.3	$0.5

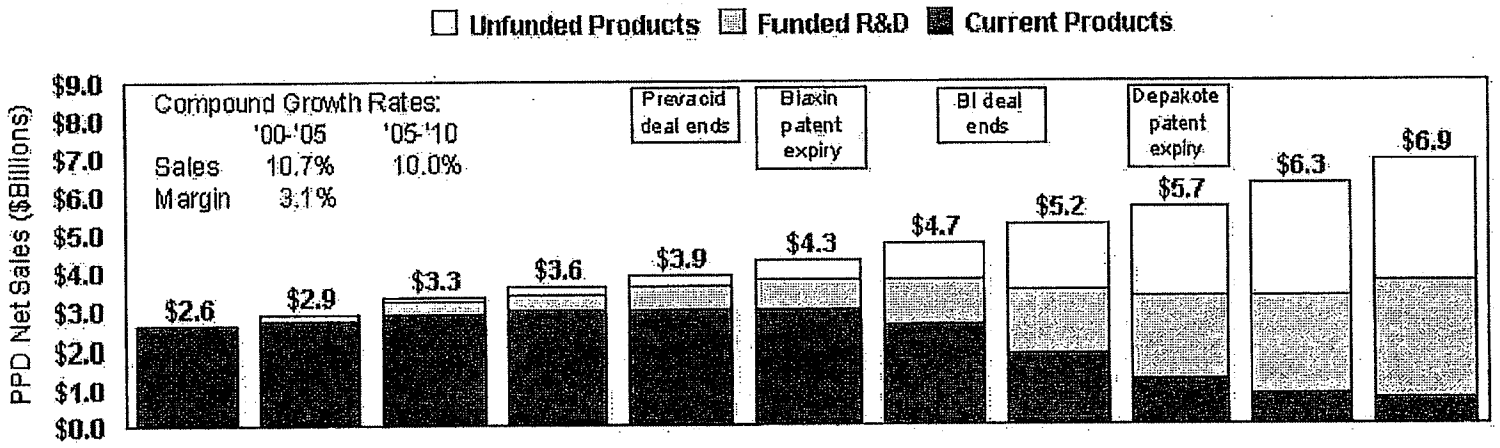
Global R&D Spending

5 Year CGR = 10%



- This rate of growth will fund the development of 11 new compounds over the LRP
- Abbott currently has 23 compounds that are in or will enter the development over the LRP

This near term lack of internally developed new products will create a larger sales and margin gap from 2005 on as patents expire for Biaxin (2005) and Depakote (2008) and deals for BI products (2006-07) and Prevacid (2004) end.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Current I	$2.6	$2.7	$2.9	$3.0	$3.0	$3.0	$2.6	$1.9	$1.2	$0.8	$0.7
Funded		$0.2	$0.3	$0.4	$0.6	$0.8	$1.2	$1.6	$2.1	$2.5	$3.0
Unfunde			$0.1	$0.2	$0.3	$0.5	$0.9	$1.7	$2.4	$3.0	$3.2

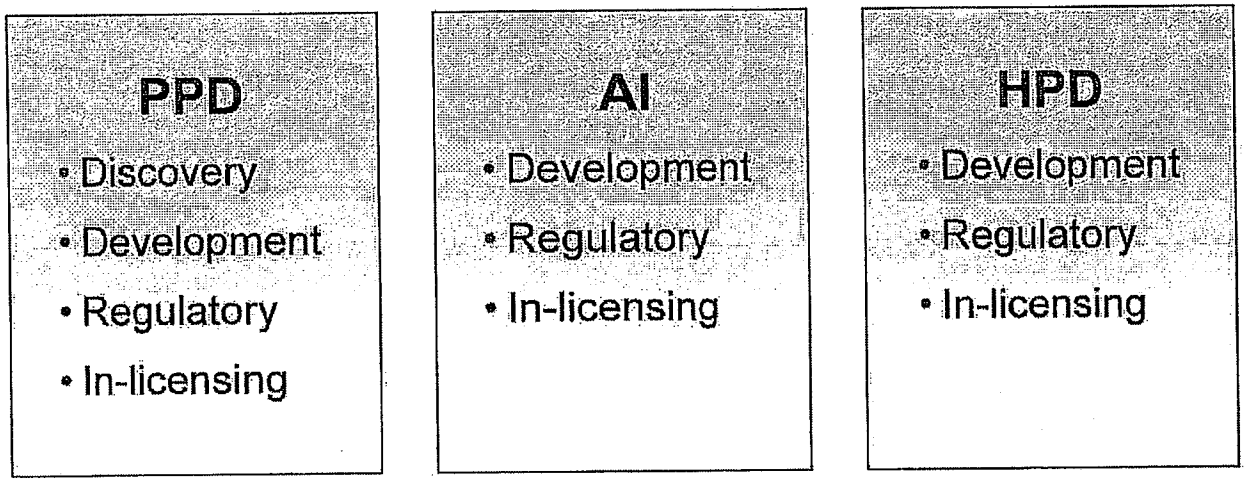
Abbott needs to launch nine new products ($350MM peak year sales) in addition to those in the pipeline to assure double-digit compounded growth over the next 10 years.

These products, whether internally discovered or in-licensed are unfunded and would cost an estimated $6 billion to develop over the next 10 years.

Summary of Abbott Pipeline Challenges

- Short term challenges
  - Lack of late stage compounds creates a short-term sales gap over the LRP
  - Emphasis on in licensed compounds decreases margin to create an even larger margin gap over the LRP
- Long term challenges
  - We will lose margin from our three major products (biaxin, depakote and prevacid) between 2004 and 2008.
  - There are not enough early stage compounds in the development pipeline to support the growth of the pharma business
  - We cannot currently afford to fund the development of the early compounds that we have

Abbott drug development is also impaired by fragmentation of the drug development and in-licensing efforts



This fragmentation:

- Produces redundant activity and spending
- Prevents efficient sharing of knowledge across the organization
- Prevents attainment of critical mass
- Makes it difficult to develop long-range global pharmaceutical strategy

Possible strategies for addressing the challenges of growing the Abbott Pharma business

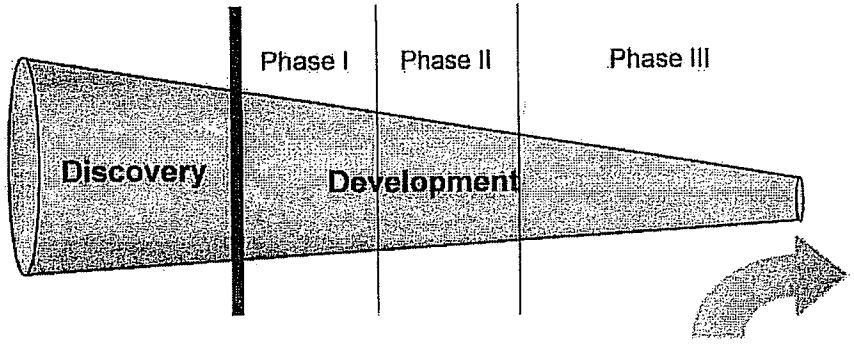
- Loading the pipeline with more late stage compounds
  - In licensing
  - Acquisition of small and mid cap biotechs
  - Co-marketing deals with other pharma companies

- Increase R and D spending to develop more early stage compounds
  - Creative deals for outside funding
    - John Hancock ($200 MM over 4 years for R and D in exchange for a royalty on developed drugs)
  - Acquisition of companies with R and D spending
  - Alliances with biotech companies that are willing to co-fund development
    - Abbott is currently pursuing such a deal with Millennium in the areas of diabetes and obesity
  - Utilize genomics and other technology advances to increase the efficiency of the R and D process

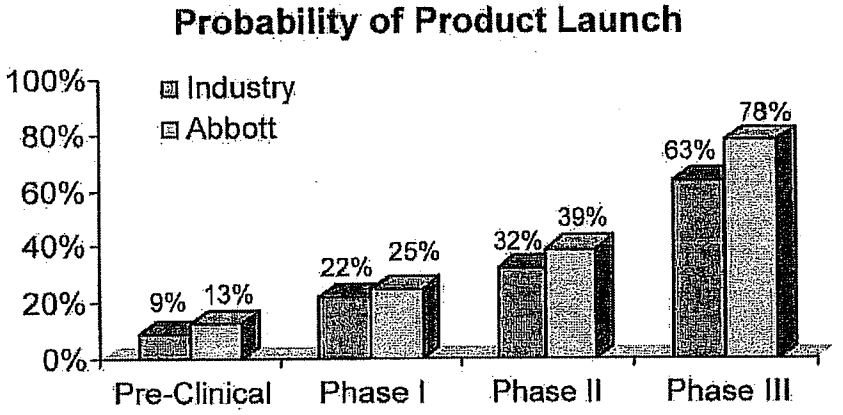
Possible strategies for addressing the challenges of growing the Abbott Pharma business (continued)

- Address fragmented R and D and in-licensing processes
  - Create integrated pharma R and D and in-licensing structures that are responsible for all drug development and in-licensing for PPD, AI, and HDP

It is becoming increasingly difficult to fill the pipeline through in-licensing and acquisitions.

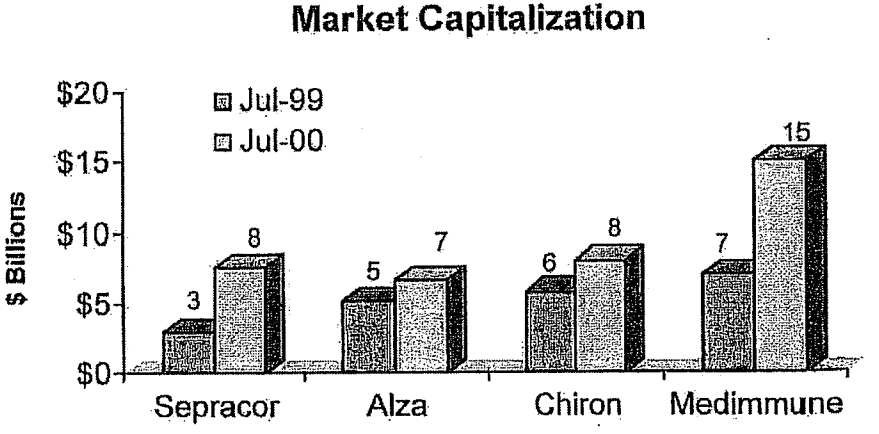


In-licensed compound jump start the development process



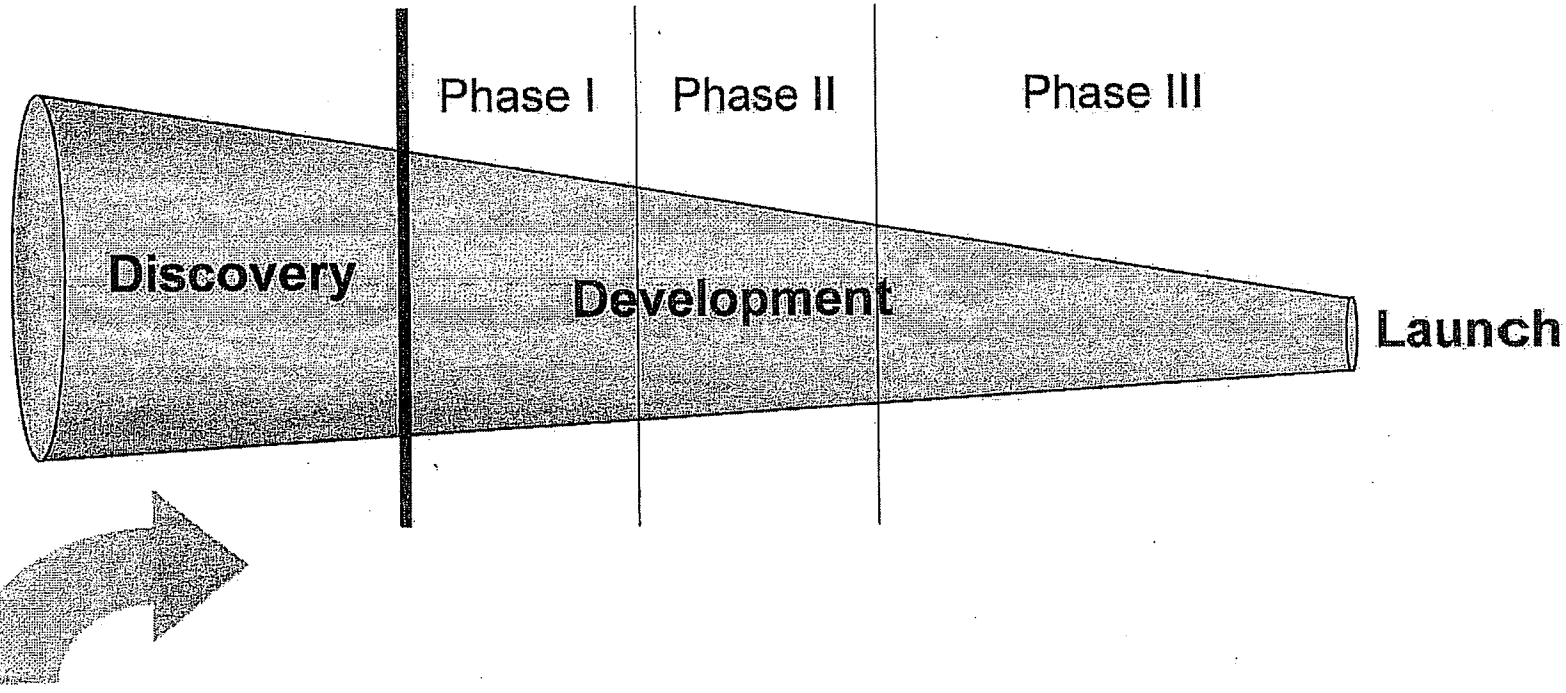
Sources: Lehman Bros., Internal Data

- Risk
  - Problems with Coactinon, FTC and Mobic highlight the risks of in-licensing
- Expense of product deals
  - Buying frenzy for late-stage products has challenged conventional valuation models
- Tactical acquisitions becoming less affordable
  - Soaring market capitalization of smaller pharma and biotech companies



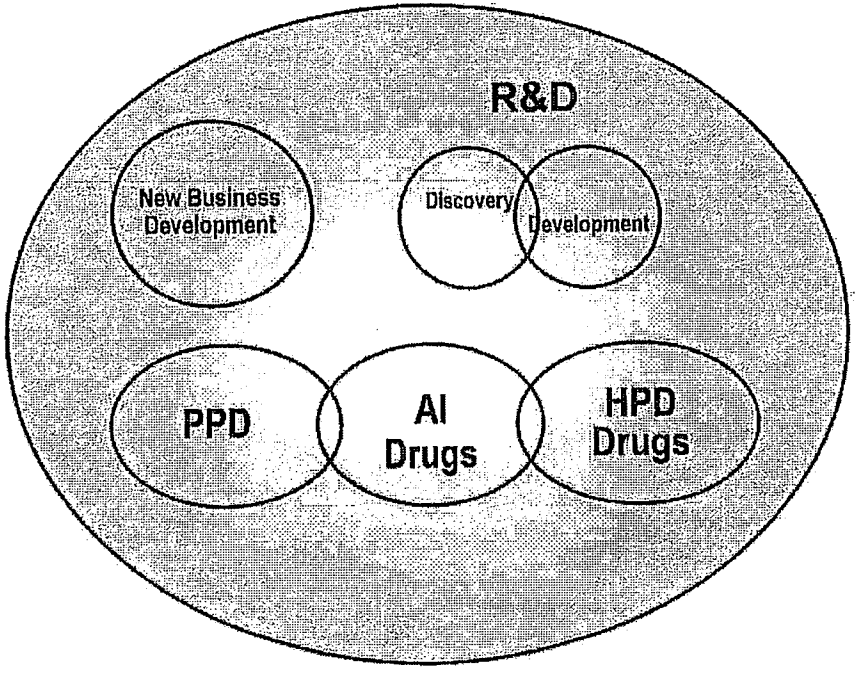
Source: Stock Market Data

Genomics is an important part of the long-term strategy but will not help fill the pipeline near-term



By identifying new "druggable" targets genomics significantly accelerates new target identification and validation but doesn't speed up development

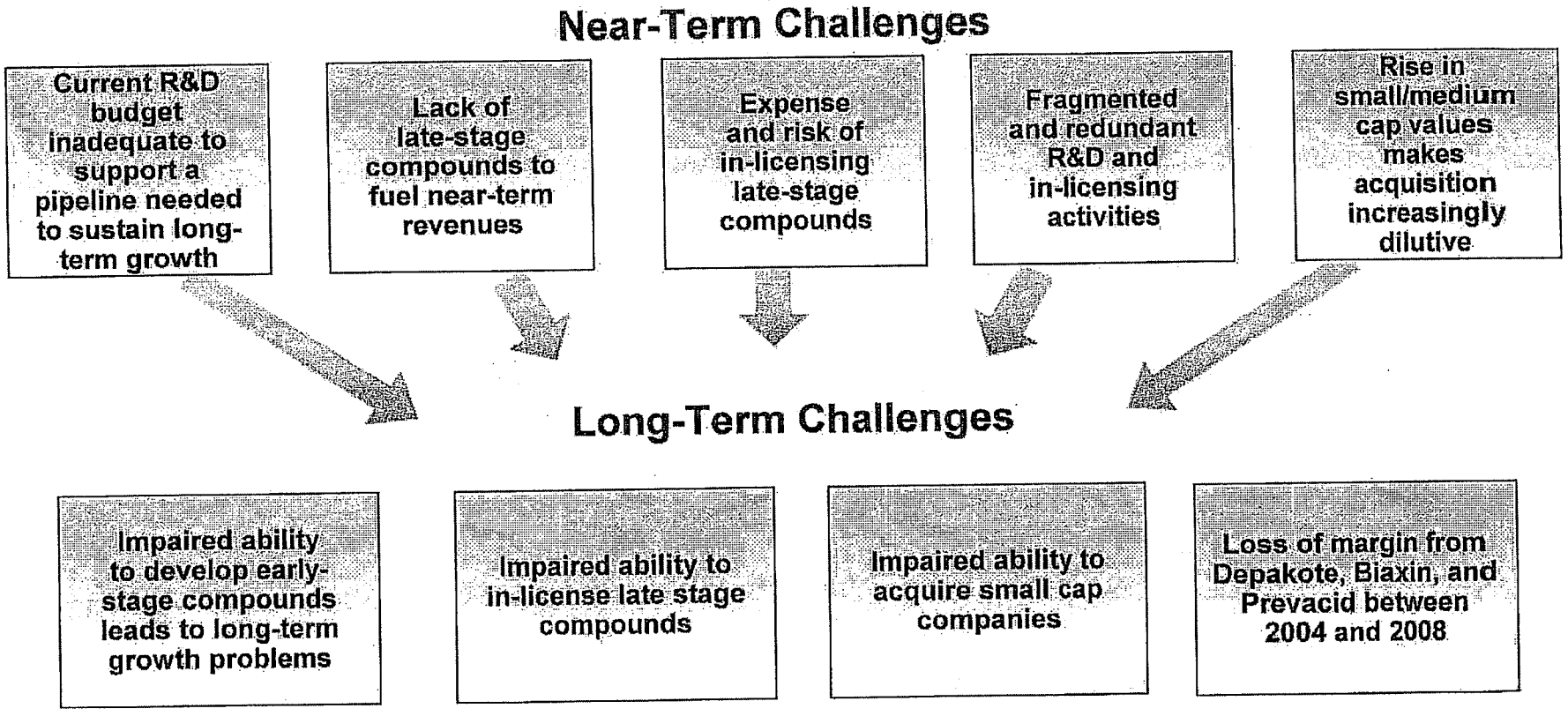
Abbott is considering integrating pharma R and D and new business development in order to address this fragmentation



Advantages

- Integrates all pharma R&D into a single unit leading to
  - economies of scale,
  - a portfolio approach to decision making and global product development
- Creates a single new business development unit to pursue global Pharma deals

Abbott faces a matrix of challenges in growing its pharma business



Conclusions:

- Improved in-licensing, R and D, and small deals for late stage compounds can be used to fill the sales gap in the LRP through 2005. However such approaches will limit margin growth over the LRP
- These traditional approaches will be insufficient to maintain sales or margins in the face of losing Depakote, biaxin, and prevacid revenues between 2004 and 2008.

This analysis suggests that a larger acquisition or merger will be necessary to successfully grow the pharma business over the next 10 years.

PLs' CW

Randomized, Double-Blind, Placebo Controlled Evaluation of the Safety and Efficacy of ABT 594 in Subjects with Painful Diabetic Polyneuropthy

The 594/M99-114 Study
Centralized Patient Recruitment Program

Abbott Laboratories

Prepared by Patient Quest

September 26, 2000

Patient Quest thanks you for the opportunity to provide this recommendation for patient recruitment for the 594/ M99-114 Study, a clinical trial being conducted by Abbott Laboratories.

The Patient Quest Approach

Patient Quest's recruitment campaign strategy is based on using a coordinated, centralized and aggressive approach to accelerating recruitment. Our full recruitment program requires the following components, each seamlessly integrated:

- Advertising development that includes an effective, well-defined advertising message for the target audience
- A comprehensive media plan that uses a systematic, centralized approach to media placement across sites
- A customized call center that will systematically prescreen callers who respond to the advertising and direct qualified referrals to the appropriate sites
- A well-designed communication plan that includes a tracking system to measure advertising effectiveness, call volume and the status of each interested potential volunteer that has qualified through pre-screening

A Patient Quest project manager, who facilitates streamlined communications between all involved persons, coordinates the program. This approach affords Abbott the benefits of multidisciplinary expertise with the convenience of 'one-stop' shopping.

This fully integrated approach offers the continual interaction between parties that is essential for an effective recruiting program. It allows for the flexibility of scheduling that is so important to the sponsor and the sites. And, it allows for the nimbleness necessary to reach and motivate a moving target – a qualified consumer – and to bring them along from 'unaware' to enrolled.

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Background, Situation

The primary objective of the Abbott 594/M99-114 Study is to compare the safety and efficacy of 150mg, 225 mg, and 300 mg twice daily (BID) ABT – 594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

This is a Phase II, randomized, double blind, placebo-controlled, multicenter study to examine the safety and efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. A total of 320 subjects need to be randomized in an equal ratio to receive 1 of 4 treatments of ABT-594.

The original enrollment period was seven months; the study began in April 2000 and completion was anticipated by November 2000. The enrollment period has been extended by four months and is now planned to close in March 2001. Approximately 160 patients were to have been randomized by 9/22 and an additional 160 are needed to complete the Phase II arm of the study. There are currently 28 sites recruiting, randomizing and treating patients.

Most sites are struggling with recruitment due to limited outreach of the sites to the target population. The study is having additional challenges with retaining participants in the study once randomized. A large percentage of the loss of these potential patients is caused by the severe nausea during the first week of treatment. Although this may not effect Phase II of this study, Patient Quest suggests that we will gain additional knowledge from the current randomized patients in order to create an effective retention program for Phase III.

Due to the challenges and low enrollment rates, Abbott Laboratories would like to assist the sites in their recruiting by providing a centralized program to supplement the Principal Investigator's efforts.

Patient Quest is proposing an approach that starts with the most targeted method, direct mail, and is supplemented by newspaper advertising.

The Target Audience

The Condition and Demographics

Diabetic neuropathy is a nerve disorder caused by diabetes, which affects 50-60% of diabetic patients. 798,000 new cases of diabetes are diagnosed every year.

Symptoms of distal symmetric diabetic polyneuropathy include numbness and sometimes pain in hands, feet or legs that occurs equally on both sides of the body. Other symptoms include

tingling, burning "pins and needles", numbness, aching, itching, and other abnormal sensations. People with diabetes can develop nerve problems at any time and the risk increases the longer a person has diabetes.

The condition appears to be more common in smokers, people over 40 and those who have had problems controlling their blood glucose levels. There are two main categories of diabetic neuropathy: diffuse, which affects many parts of the body and focal, affecting a specific nerve and part of the body. Pain is associated with both types.

Prevalence of diabetes by age:

- 65 years or older: 6.3 million (18.4 percent of all people in the age group have diabetes)
- 20 years and older: 15.6 million (8.2 percent of all people in this age group have diabetes)
- Under age 20: 123,000 (.16 percent of all people in this age group have diabetes)

Prevalence of diabetes by sex:

- Male 7.5 million (8.2 percent of all men have diabetes)
- Female 8.1 million (8.2 percent of all women have diabetes)

Prevalence of diabetes by race-ethnicity in people 20 years or older:

- Non-Hispanic whites: 11.3 million (7.8 percent of all non-Hispanic whites have diabetes)
- Non Hispanic blacks: 2.3 million (10.8 percent of all non-Hispanic blacks have diabetes) On average, they are 1.7 times as likely to have diabetes as non-Hispanic whites of similar age.
- Mexican Americans: 1.2 million (10.6 percent of all Mexican Americans have diabetes) On average they are 1.9 times as likely to have diabetes as non-Hispanic whites of similar age.
- Other Hispanic Latino Americans: On average, Hispanic/Latino Americans are almost twice as likely to have diabetes an non-Hispanic whites of similar age.

Media Recommendation

Direct Mail

Using the sites/zip codes provided, a search was done of lists for persons with diabetes who live within a 30 mile radius of each investigative site. This search turned up a total of 59,114 names. Names were only gathered for people within the 30-mile radius, as past experience has taught us that this is the approximate distance that consumers are willing to travel – particularly if they live in major metro areas. (This distance is greater if they live in a more rural area, or by disease/condition: the greater the pain or threat, the more willing they are to travel longer distances.)

The direct mail piece will be sent via first class mail to households where one or more family members are diabetic. The envelope will be attractively designed and will carry a headline that compels the recipient to open it and read the contents. The headline will be based on research with that target audience. The use of first class stamp and ink jet address will differentiate the mailing from mass-market "junk mail". The inner content will consist of pertinent trial information and a dedicated toll-free number. We will also include a bookmark, with basic study information and toll-free number that can serve as a handy reference or be passed onto a potentially eligible friend.

The list is broken out by market as follows:

Investigator	City / State	Zip Code	Count
Backonja	Madison, WI	53792	665
Baumel	Miami, FL	33154	3,266
Baumel	Boca Raton, FL	33486	1,470
Biton	Little Rock, AR	72205	1,531
**Bromberg	Salt Lake City, UT	84132	1,227
DeBold	Minneapolis, MN	55416	2,300
Drucker	Clearwater, FL	33761	3,940
Eisner	Ft Lauderdale, FL	33321	-
Forde	Syosset, NY	11791	3,211
Fried	Providence, RI	2907	1,602
Gibson	Little Rock, AR	72205	-
Gleeson	Albuquerque, NM	87108	756
Haag	Springfield, Ma	1199	2,012
Hewitt	Atlanta, GA	30322	3,692
Holmlund	Buffalo, NY	14209	3,436
Kafka	Altoona, PA	16602	1,205
Kafka	Duncansville, PA	16635	
**Kipnes	San Antonio, TX	78229	2,958
Kirby	Peoria, AZ	85381	3,030
Kluge	Fort Meyers, FL	33916	1,903
McGill	St Louis, MO	63110	3,285
Rowbotham	San Fransisco, CA	94115	851
Shaibani	Houston, TX	77030	4,389
Simmons	Hershey, PA	17033	2,172
Singer	Pembroke Pines, FL	33028	-
Sivakumar	Phoenix, AZ	85013	-
Steel	Greenville, NC	27834	1,254
Storey	Albany, NY	12205	1,046
Suri	Dinuba, CA	93618	2,063
Vinik	Norfolk, VA	23510	2,918
Weinstein	Walnut Creek, CA	94598	2,932
Total			59,114
**These sites have indicated to sponsor that they do not wish to participate in a centralized program but have been included in the event of a change of mind			
Counts with zero have like geos with other sites so data with be divided among the duplicate sites			

General Media Support

Newspaper is the strongest general consumer media for delivering 40+ adults locally – our primary target group for Diabetics. Heavy users of newspapers in this age group index at 119 – meaning they are 19% more likely than the rest of the population to be every day readers of newspapers. Medium users (every other day, 3x/wk) index at 130. There are also newspapers available for minority populations, both Hispanic and African American. The disadvantage to newspaper is that while it has immediate delivery (same day response), it does not build awareness as quickly as broadcast media such as TV or radio.

Television is the second strongest media, with heavy users in the 40+ group indexing at 115 and medium users at 107. As with newspaper, there are select stations or programming to deliver minority populations. The disadvantage to television is that while is can very quickly build awareness, it requires longer lead time and greater frequency.

We would recommend launching with newspaper at a 3+ frequency – meaning the advertisement should run a minimum of three times before it could deliver effectively. A combination of general and minority publications would be used in markets with large minority populations. All newspaper should start within a week of the first direct mail drop, and then pulse out once a week thereafter. If we find after the first insertions that newspaper is not pulling adequate responses then we would consider switching over to television for the last week. However, we do not believe that this will be necessary.

Newspaper in these markets at a 3x Frequency, 30% Reach should generate around 5,000 calls and cost $300,000 - $350,000.

Recruiting Premise and Assumptions

Patient Quest has developed an outcome model to project candidates' interest in, qualification for, and enrollment in this study. This model is based on past recruitment experience, as well as a number of subjective factors, including:

- Degree of advertising effectiveness relative to the volunteer's interest in participating in the study
- Percentage of volunteers' advertising awareness required to generate the anticipated number of calls
- Volunteer's receptivity to the program and ability to meet inclusion criteria

This outcome model includes a proforma *recruitment funnel* that allows us to estimate the volume of total contacts necessary to reach the enrollment goal of 160 outpatient volunteers with diabetic polyneuropathy. When developing the funnel we take into consideration inclusion/exclusion requirements, as well as general population incidence and disease awareness.

The Funnel

At various response rates, the mailing to 59,114 diabetics would generate the following call volumes. Based on past experience a ½ percent ratio is the most likely scenario. We would expect approximately 5,000 calls from the newspaper advertising based on a 1% response rate.

Anticipated Response

@2%	@1%	@1/2%	
6,180	3,090	1,545	Total calls generated *Hang up (25% lost)*
6,885	3,442	1,721	Balance *Fall out after learning about trial (25% lost)*
5,163	2,581	1,290	Balance *Fallout for failure to meet inclusion criteria (70% lost)*
1,549	774	387	Balance *Half are no shows (50% lost)*
774	387	193	Show up for appointments *Do not qualify based on PI (50% lost)*
387	193	96	Enrollees (40% of which will drop out in week 2)

Call Center

Importantly, once the advertising has begun to generate responses, Patient Quest will coordinate responder screening and referral of pre-qualified candidates. The Call Center will develop the operator script and tracking process at the same time that the message development is being done. This means that all potential consumer communication can be submitted to the IRBs as a package.

During the day all calls will be answered by a healthcare professional. An Interactive Voice Response (IVR) back up will be available in case of overflow. The IVR will also be in place after hours. The IVR will take the responders name and best time to return their call, so an outbound call can be made the following business day.

Patient Quest will also provide the sites with information about the recruiting effort and will stagger the intensity of the recruitment effort to meet their needs. This will prevent sites from being over-whelmed with candidates and will allow them to prepare for appointments. Responder and referral reports will be generated on a regular basis for Abbott and for the sites. The objective is to coordinate the Direct Mail/Print Advertising with the site's abilities to process patients and Abbott's need to enroll quickly.

Media Planning, including the release of the Direct Mail, is carefully coordinated to meet both site requirements and efficient call center staffing. The Call Center is notified when a mailing is posted, as is each site.

Creative Development, Research and IRB Submission

A series of 'concept messages' will be developed. These messages will explore the full spectrum of rational and emotional ideas that could motivate a consumer to consider participation. The concepts, in the form of mock-ads, will be exposed to the target audience in focus groups.

Once the groups are completed, the concept that generates the most interest and prompts the most willingness to consider participation will be translated to a Direct Mail piece and to a newspaper ad. The same tonality and language will be reflected in the Call Center script.

Project Management and Coordination

At the core of Patient Quest's Recruitment Program is a dedicated team of individuals with the experience to execute complex and coordinated tasks. A senior project manager will oversee the day to day operations with the assistance of a project manager, a project coordinator and an administrative assistant. This style of management provides the flexibility required to effect changes in the program as needed.

A Patient Quest-designated team leader will coordinate all activities for the recruitment program and will serve as the primary contact for Abbott. In addition to telecommunications, the project manager will provide continual updates, by fax or e-mail, of all recruitment activities.

The following describe project management duties that are performed by the project manager or a supervised designee:

Site Interactions
The project manager will coordinate all site communications. Since the trial in already in progress, a letter of introduction will be sent to the sites along with a fast-fax questionnaire. The site responses facilitate communication and help us to efficiently tailor this recruitment program to their needs. Information we request includes:

- Verification of contact information with the site
- Is there a staff member dedicated to calling referrals
- Site hours—best times to call
- If fax machine is left on at night
- Geographic distances within which each site believes it can accommodate study volunteers
- Referral volume the site can handle (management of the flow and processing of referrals)

The project manager will also work closely with the sites for submission of advertising and direct mail pieces to the IRB. A database will be set up to track IRB approvals to ensure that no ad placement or mailing occurs without written documentation of IRB approval.

The project manager will also implement a referral tracking process. A Referral Status Worksheet will be created in cooperation with the call center and sent to the sites on a weekly basis. The worksheet will list the names or initials, date of birth, and gender of the qualified referral; ad type; date of prescreening; and date of the first scheduled appointment, if known. The worksheet provides space for the site to indicate that they have contacted, scheduled, or have seen the

referral. Tracking is continued until the referral is enrolled into the study or disqualified by the site. There is also room to provide comments. All information, except volunteer names, will be shared with Abbott on a weekly basis. The record of progress for each referral lends valuable insight into site performance and gives early clues about potential areas of concern, particularly scheduling problems. Metrics can also be developed, including referral-to-enrollment rate and cost-per-referral. Patient Quest can customize the Referral Status Worksheets and all related reports to Abbott's specifications. The frequency of worksheet distribution and reports is at Abbott's discretion.

Call Center Activities

The project manager will provide Abbott with updated accounts of responses to advertising activities.

Media Placement

The project manager will be responsible for submitting all orders for media and for communicating any changes to the plan. Abbott will authorize all media expenditures prior to each media buy. A personalized letter will be sent to each study site to provide advance notification of the mailing or advertising being placed on behalf of that site. The appropriate Abbott team members will be copied on these notifications.

Conference Calls

A critical component of our project management services includes scheduled weekly conference calls throughout the recruitment period. These conference calls will include key Abbott and Patient Quest personnel, when appropriate. The purpose of the conference call is to keep all team members up-to-date on the status of the recruitment program, identify any problems, offer solutions, review call center reports and operations, and evaluate the advertising response rate. Conference call summary reports (service reports) will be written and faxed to all team members within 48 hours of each conference call.

Client Services

The project manager will update Abbott on all activities by phone, fax, or email. The following reports or communications will be sent to Abbott throughout the recruitment period: service reports after conference calls, IRB tracking updates, referral status reports, and metrics summaries.

Timeline

This recruitment program will require an aggressive approach. Patient Quest will develop the advertising message through primary research with the target audience, and will work with IRB comments to ensure motivating and approvable advertising. Our goal is to start the Direct Mail effort in early November, which allows six weeks for creative development, research and expedited Western IRB approvals. Supplemental newspaper advertising will follow as quickly as possible, but should start after the presidential election (Nov. 7) and should avoid the week of Nov. 20 (Thanksgiving).

September, 2000

- Proposal for Recruitment Program submitted to Abbot

October, 2000

- Authorization to begin
- Final budget prepared and contract executed
- Call guide development/approval
- Creative Development for advertising
- Concept refinement/ develop prototype ads
- Conduct qualitative research (one-on-one interviews)
- Develop final direct mail and newspaper ad
- Finalize Media Placement
- Expedited IRB approval of newspaper ad, direct mail piece, and Call Guide for Western IRB sites
- Call guide programming
- Call guide testing
- Telecommunications training
- WIRB approved materials to Private IRBs

November, 2000

- Direct mail produced and mailed
- Newspaper advertising begins
- Weekly media reports issued
- Tracking of status of qualified referrals with each site begins

December, 2000

- On going patient recruitment, tracking, and enrollment

January, 2001 - March, 2001

- On going patient recruitment, tracking, and enrollment

Budget

1. Creative & Media	$ 456,000
2. Project Management and Coordination	$ 66,250
Direct Mail Campaign Operational Costs	$ 48,980
3. Miscellaneous Expenses	
(FedEx, travel to CT, mess. etc.)	$ 3,000
4. Call Center Costs	$ 95,970
Total Program	$ 670,200

1. Assumptions & Detail – Creative, Research & Media Costs	
Strategic Planning & Program Development	$ 7,500
Concept Message Development	$35,000
Research Out-of-Pockets: Two focus groups in Ft. Lee, NJ	
With Diabetics	$20,000*
Final Production, Mechanicals/Photography	
Direct Mail Piece	$15,000*
Newspaper Advertisement (Qtr Page, B&W)	$15,000*
Media Planning & Negotiation	
10 Hrs/Market, 26 Markets	$32,500
Media Implementation, 5 months @ $5,000	$25,000
Newspaper Ad Materials	$ 3,500*
Media Financial – Tracking, checking & billing @ $500	$ 2,500
Media Space	$300,000**
Total:	$456,000

*Research and Production costs will bill out-of-pocket costs as actual with no mark-up. Estimates are ± 10%.
**Media will bill at Net + 5.4%, (Gross - 9.6%). The 5.4% covers all buying fees.
**Media buy for only markets with low list volume -- approximately $100,000

2. Assumptions & Detail – Project Management and Coordination	
Total Start up Costs	$ 16,250
Total Management Fee -	$ 50,000
Total Project Costs	$ 66,250

Start-up costs $ 16,250

- Site communication and data collection: includes letter of introduction and fast-fax questionnaire
- programming data management systems with site specific information, including referral tracking database, IRB approval database, and site communication database

Management $ 50,000

(Assumes 5 month recruitment period)

- Managing direct mail campaign, including list procurement
- Oversee production and mailing
- Manage and track IRB approvals
- Referral tracking
- Project coordination
- Administrative duties
- Conference calls
- Updates on IRB approval tracking
- Referral tracking and status reports

Estimated Operational Costs for Direct Mail Campaign $ 48,980

Operational costs are to be billed on a monthly basis as incurred with no mark-up.
Postage, mailing list and start up costs must be pre-paid before mailing

Estimated Printing direct mail pieces 59,000	$ 8,850
Estimated Mailing direct mail pieces 59,000	$ 2,955
List purchase 59,000 names	$13,050
1st class postage 39,000 @ $0.33	$19,470
Affix stamps 59,000	$ 2,655
Phone, fed Ex, fax $400/month for 5 months	$ 2,000

3. Assumptions & Detail on Call Center Costs:

Total Start up Costs	$ 8,620
Total Operational Costs	$82,250
Total Fulfillment (Optional) $5,100-$5,275	*$5,100*
Estimated Total Project Costs	$95,970

- Since it is difficult to forecast actual call volume, shared healthcare professionals will be used to answer inbound calls for the Abbott Study.
- For purposes of this proposal a 3% return on a mailing of 181,368 supported by advertising is estimated, 5,000-6,000 calls over three months.
- The support of the studies is to begin June 2000, continuing over 3 months.
- Advertising, direct mail efforts will produce enough qualified leads for the sites to complete the enrollment within the designated period.
- The study will be conducted at approximately 21 Investigative Sites
- Patient Quest will refer patients to the site closest to them geographically
- Patient Quest will establish 2 toll free numbers; one for potential participants, the other as a toll free fax line
- Patient Quest will deliver all data on the central screening effort in an agreed to format and maintain the database of callers for future use by Abbott.
- 100% of the after hours callers will go to a Voice Mail for a return call the next business day.

Call Center Role:

- Acquisition and reservation of the toll free numbers
- Design the live call guide with branch logic paths
- Creation of a database and transcription of participant responses
- Development of Standard Operating Procedures
- Creation of database of the investigative sites
- Daily review of the inbound and outbound telemarketing results
- Deliver database to Abbott in designated format at project completion
- Provide inclusion/exclusion questions to qualify for the study.
- If qualify refer to a study and capture information
- If caller does not qualify to ensure confidentiality and support
- Enhance the quality of the consumer interface
- Implement innovative techniques for building consumer trust
- Identify effective and cost-efficient mechanisms to put goals into practice

Selected types of calls, media inquiries or escalated complaint calls, will be transferred to Abbott core internal team.

Start up Costs

Project Design Management: 30 hours @ $85 per hour $2,550

The Patient Quest Call Center – Project Manager will manage every aspect of launching the telemarketing program with the call center and act as a point of contact for Abbott on call center related issues.

- Conduct all training sessions

- Quality assurance checks on all systems, call guides, reports, and
- Design the monitoring program
- Team Strategy and Tactics meetings and conference calls
- Data input on protocol and sites
- Design of inbound call guide
- Sponsor database integration planning
- Creation of outbound call guides
- Modifications to call guide after Abbott and IRB review
- Database development
- Report design
- Training design

Programming: 30 hours x $95 per hour $2,850
- Program Automatic Call Distributor for call allocation
- Program database fields and criteria questions
- Program logic sequence
- Program call guide
- Program data files to generate data transfer to site
- Program report formats
- Establish loop to database
- Establish after hours voice mail and transcription
- Input all information about investigative sites

Communicator Training: $2,720
Design and implementation
6 Nurse Communicators x $40 x 8 hours = $1,920
1 Supervisor x $50 x 8 hours = $ 400
1 Project Manager x $50 x 8 hours = $400

Clerical Support $ 500
- Clerical work related to establishing the training program and manuals
- Faxing and copying time
- Any other special customer service provided on behalf of the client

Total Start Up Costs $ 8,620

Operational Costs
Project duration will be 5 months

Estimate Shared Healthcare Operators – Inbound Service $65,000
Calls are estimated to last an average of 8 minutes including any wrap up time spent in the call guide. Calls are billed at $1.50 per minute for Nurse Communicators. This includes Telecom, call floor supervision and mpr charges.
Estimate between 5,000 and 6,000 calls over a 5 month time period x 8 minutes x $1.50/min.
5,000 calls x $1.50 x 8 minutes = $60,000
6,000 calls x $1.50 x 8 minutes = $72,000

Monthly minimum labor fee for the Nurse hours of shared coverage = $8,000/month.
When call volume fees exceed the monthly minimum, total-calling minutes in the shared environment will be billed at the $1.50 per minute fee.

Project Management: 20 hours/month x 5 months x $85/hour $8,500
- Review of media and call guide effectiveness
- Strategy sessions on telemarketing activity
- Participation in client meetings and discussions on site follow up performance
- Oversight of daily and monthly reports
- Oversight of monitoring
- Weekly review of project results and telemarketing productivity

Clerical Support: $100 each month X 5 months $ 500
- Clerical work related to data transfer of screening sheets
- Faxing and copying time
- Any other special customer service provided on behalf of the client

Database & Fulfillment Mgmt: $1,500 each month X 5 months $ 7,500
- Addition and deletion of sites
- Modifications to the call guide
- Daily reports
- Links to fulfillment processing
- Arrange coordination of inventory
- Coordinate printing and quality control processes
- Institute delivery parameters and most efficient delivery process
- Final project summary

Estimate Welcome Letter $ 500
Estimate mailing 500 pieces to follow up on phone contact to qualifying participants:
Custom letter plus up to 3 inserts placed into an envelope @ $0.65 -
$1.00 each + $0.55 postage (pass through cost)
500 x $0.65 = $325
500 x $1.00 = $500

Postage will be billed at pass through cost
500 x $0.55 = $275

Facsimiles: Estimate 500 faxes x $.50 per fax $ 250
- Daily schedules, patient screening forms, patient tracking forms

Operational Costs $82,250

PLs' CZ

Clinical Trial Recruitment and Centralized Screening Program For Painful Diabetic Neuropathy

Developed for Abbott Laboratories
September 28, 2000

Executive Summary

Abbott Laboratories is conducting a multi-center, randomized, double blind, placebo-controlled study investigating the efficacy and safety of ABT-594/M99-114 in subjects with painful diabetic neuropathy (PDN). To date, 29 U.S.-based clinical research sites have accrued approximately 151 of the needed 320 patients. The deadline for enrolling the balance of 169 subjects has been extended until March 2, 2000. Study centers will continue to use site-directed methods for recruitment, so it is anticipated that additional patients will be accrued by sites over the next five months.

In an effort to complete enrollment by the March deadline, Abbott Laboratories has asked Phone Screen (a medical call center specializing in clinical trial recruitment) and its partner GCI Healthcare Clinical Trial Recruitment (a subsidiary of Grey Worldwide which implements marketing-oriented recruitment acceleration initiatives) to develop recommendations to maximize timely delivery of the needed study subjects. As Abbott anticipates that the sites will deliver about 69 patients on their own, the recommendations are designed with a recruitment goal of approximately 100 additional subjects. Abbott has stated that the current 34% dropout rate is considered in this goal number.

Key Enrollment Challenges

While painful diabetic neuropathy is a debilitating condition that has a significant impact on quality of life, study sites are confronted with a number of issues that have affected subject accrual. These issues include:

- High study dropout rate of 34% primarily due to side effects of the investigational drug
- High level of screen failures (50%)
- An older population cohort (as defined by the incidence of PDN) resulting in medical exclusion due to co-morbidities
- Other restrictive inclusion/exclusion criteria
- A general unwillingness by otherwise qualified candidates to washout of pain medication the week prior to start-up
- Patients are hesitant to participate in a placebo-controlled study
- Ongoing competitive studies at the study site or within the study market, all vying for the same patient pool
- Diabetic neuropathy is often undiagnosed by PCPs who are the primary manager of people with diabetes

Key Learnings from Study Sites

During preparation of this proposal, GCI Healthcare contacted three study centers (Dr. Backonja's site, Dr. Gibson's site and Dr. McGill's site) to benefit from their insights on recruitment for this study. The following represent key learnings from these conversations:

- Study sites feel that radio ads will be successful in reaching potential study subjects
- The typical study subject is a retiree
- Primary motivators for entering the study are:
  - Desire for pain relief
  - Free study medication
  - Compensation for study visits
- Patients often express satisfaction with their current pain medication without realizing that they are most likely not getting much pain relief, and the Abbott study may provide the opportunity for improvement.

These insights will help drive the creative direction for development of the radio ad.

Program Strategy

- To use proven communications vehicles to generate a high volume of pre-qualified referrals in the shortest time possible
- To minimize time spent by site personnel in early screening phases of recruitment, allowing them to focus their efforts on only the most qualified candidates
- To establish excellent relationships with the study sites in order to foster an atmosphere of commitment and responsibility to the study
- To develop and implement a referral management and tracking system to ensure that all leads are processed in a timely manner

Summary of Tactical Execution

Phone Screen and GCI Healthcare have developed an accelerated recruitment program, which relies on the following Core Program components:

- Radio advertising
- Centralized call center that will manage and track all referrals from the radio ads
- Targeted direct mail component
- Study site and IRB relations
- We have also recommended a Direct Mail Campaign and "pilot" Physician Referral Expansion Program as a supplementary effort for consideration by Abbott.
- Market Mapping

These recommendations are designed to provide aggressive recruitment support to 29 of the 30 study sites, as requested by the Abbott Team. However, based on the available budget, Abbott may wish to support a select subgroup of these 29 sites. In an effort to assist with the selection process, GCI Healthcare has tentatively ranked the sites (Tier 1, Tier 2 or Tier 3) based on:

- Readily available data relative to diabetes prevalence
- The number of study sites in each market – giving higher priority to metro areas with multiple sites
- Areas with higher number of retirees

Refinements to this ranking may be necessary, as Abbott may have insights about specific study sites. GCI has built additional market mapping research into the budget.

Budget

The attached spreadsheet, which itemizes the budget, assumes that advertising support will be provided to all 29 sites. Once Abbott is able to determine how many sites to support, a final budget will be submitted.

Conclusion

Phone Screen and GCI Healthcare are poised to move forward upon approval of these recommendations and look forward to working with the Abbott Team as the study moves forward.

Recruitment Estimate Funnel

GCI Healthcare estimates that the recruitment program will need to generate 2,500 calls to the 800 number in order to meet the enrollment goal of 107 patients. The estimation of call response is determined using a funnel with dropout rates anticipated at several junctures along the way. The following are our assumptions and rationale for our call response estimates:

- **Adults age 50+ in study markets with diabetes: (1,867,865):** This is the total number of adults age 50+ with diabetes who reside in markets in which the study is being conducted.
- **Adults age 50+ in study markets with diabetic neuropathy 45%: (840,539):** Of the total number of adults age 50+ with diabetes who reside in the study markets, we estimate that 45% have diabetic neuropathy.
- **Adults age 50+ in study markets with painful diabetic neuropathy 10%: (84,053):** Of the total number of adults age 50+ with diabetes/diabetic neuropathy who reside in the study markets, Abbott has estimated that 10% have *painful* diabetic neuropathy.
- **Advertising will reach 50% at least three times: (42,026):** This is the proportion of patients 50+ with painful diabetic neuropathy residing in the study markets who will be exposed to the radio ad 3 or more times. Three exposures are considered a minimum level for generating a response. The calculation excludes those who are exposed only once or twice. The rationale is that the first or second exposure to the ad raises awareness of and interest in the message in preparation for taking action – in this case, calling the toll-free study number.
- **Estimated call response rate 6%: (2,552):** A number of motivational and situational, as well as health, factors influence an individual's response to a clinical trial recruitment advertisement.
- **Estimated # of qualified responders/referrals from phone pre-screening 10%: (252):** This factor is based on expectations that 1 out of every 10 callers will be a potential patient presenting with symptoms and medical history that meet pre- screening criteria.
- **Estimated # attending site screening 85%: (214):** Of the patients who pass the telephone screening an estimated 85% will attend the screening appointment at the clinical research site.
- **Estimated # of screen failures 50%: (107):** Abbott has estimated that half of the patients who are screened by study sites will not qualify based on exclusion/inclusion criteria.
- **Number of randomized subjects: (107):** According to the screen failure rate provided by Abbott, we anticipate that half of the patients who are referred to a site will pass the screening visit and ultimately enroll in the trial.

Core Program Elements

Radio Advertising Campaign
The advertising period would be January through March 2000 with creative development, IRB approval process, media planning and study site relations beginning immediately upon Abbott's approval to move forward.

The media strategy is to utilize radio to effectively reach the defined target audience (see below) using specific programming. Radio has been selected because of its sense of urgency, high frequency message exposure, affordable, efficient geographic coverage of the current study site list, and ability to target the audience through station format selection.

Strategic format selection is a key component in the success of a patient recruitment campaign. News and talk formats will be utilized for several reasons:

- Services well the target demographic
- Possesses active listenership – foreground, not background
- Typically yields an excellent patient response
- Feature health reports as part of their shows
- Well-known show hosts offer credibility to their sponsors

In addition, stations that play music, which appeals to the appropriate demographic audience, will be chosen to ensure effective targeting.

The media target audience for this recruitment program has been defined as:

- Adults age 50+ (with equal media weight given to men and women)
- Broad income category, but with a primary focus on those with fixed incomes or limited financial resources
- Some media weight will be applied to stations reaching English-speaking Hispanic and African American populations in relevant study markets, given diabetes prevalence

The media planning strategy includes the purchase of 15 spots per week on 2 stations for each study market for each broadcast week. However, please note that we are not recommending radio advertising for the Syosset, New York study site for the following reason: The target study population in and around Syosset will be listening to stations that cover the entire New York metro area. As New York is the one of the most expensive radio markets in the U.S., purchasing air time would not be expected to provide a meaningful return on investment unless there were multiple sites throughout the metro area – and only a very small portion of those reached by the ad will be willing to travel to Syosset.

Commercials will air Monday through Thursday only, when patient response is typically strongest. Spots will run primarily between the hours of 10 AM – 3 PM. Purchasing spots aired during specific programs during the morning and afternoon drive times may also be appropriate for some sites. It is recommended that the schedule run simultaneously for 4 weeks in each market separated by a 2-week hiatus. This hiatus allows study sites to follow-up on referrals and provides a more controlled referral volume so they will not feel so overwhelmed. However, depending on initial communications with the sites, this can be adjusted to fit their ability to process leads. During the hiatus weeks, Abbott/ Phone Screen/ GCI Team will evaluate the productivity of the first ad weeks.

Core Program Elements – continued

The radio ad script will be written to help potential study candidates, their spouses or significant others, self identify. It will utilize a strong call-to-action, and all ads will carry a single toll-free number. We expect that even with targeted messages and media planning that there will be a significant number of disqualified callers, due to the rigors of the protocol. Sites will be advised that referrals generated through advertising are potential "leads" and that that the purpose of the centralized telephone screening is to weed out those who are obviously inappropriate (e.g. inappropriate symptoms or medical history) for the study.

Implementation Logistics:

- Develop a 60 second radio script for approval by Abbott and the central and local IRBs
- Oversee production and distribution of the radio spot
- Direct media planning
- Collaborate with Phone Screen on Call Center Activities and Reporting
- Communicate with sites to announce media plans in their local markets

Tentative Tier One (highest priority) markets for radio advertising include:

- Fort Lauderdale, Pembroke Pines, and Miami/ Boca Raton
- Atlanta
- Clearwater
- Fort Myers
- Houston
- Minneapolis
- Phoenix, Peoria
- San Francisco, Walnut Creek
- St. Louis

Tentative Tier Two markets include:

- Albany
- Albuquerque
- Buffalo
- Hershey
- Norfolk

Tentative Tier Three markets include:

- Altoona, Duncansville
- Dinuba
- Greenville
- Little Rock
- Madison
- Providence
- Springfield

Centralized Call Center

The centralized call center is the locus of all patient response activity. It removes the burden of pre-screening potential volunteers from the study site personnel and provides referral services to the study sites. The call center accepts and screens all calls made to the study specific toll-free number in response to recruitment advertising. The call center will track specific recruitment matrix and provide referrals directly to the study sites.

- **Call Center Set-up**: Phone Screen project team will design and establish customized systems for call processing. These systems include call guide development and programming, toll free number(s) acquisition and set up, and programming of clinical research site contact and location information.
- **Live Operator Service**: Phone Screen's patient recruitment specialists will be available to speak with patients "live" from 7am – 10pm central standard time. Aided by a computerized call guide, Recruitment Specialists screen callers according to the protocol inclusion-exclusion criteria. Calls received after hours (10:01pm- 6: 59am) will be captured by a study-specific voice mail and followed up on the next business day.
- **Project Management**: Phone Screen provides project coordination and staffing services, manages data management systems, data storage, back up, and document management. A project team will be formed to ensure timely and thorough responses to the needs of the project partners. Key staff involved in Project Management includes:
  - **Project Manager**: Day-to-day management of the project and project team.
  - **Project Assistant**: Administrative support including data entry and report processing.
  - **Shift Supervisors**: 24-hour supervision of Recruitment Specialists.
- **Training**: Phone Screen and GCI will schedule a specialized training program for all recruitment specialists who will service the PDN study. The training program will include a review of: diabetes and PDN, study protocol, inclusion/exclusion criteria, screening questionnaire, likely callers, handling difficult callers, frequently asked questions, and referral procedures. The Abbott Team will be invited to participate in the training.

Reports

Reports provided by Phone Screen will be used to provide sites with detailed patient information, track patients through the enrollment process and summarize critical study data. Several report options are listed below. Customized reports are also available. SAMPLE REPORTS ARE ATTACHED.

- **Patient Screen:** Daily report detailing patient responses to screening questions and appointment times. A patient screen report for each pre-qualified caller will be faxed or e-mailed to the appropriate research site (depending on site preference).
- **Referral Tracking Worksheet**: Weekly worksheet sent to research sites to obtain status of referred patients. Information is summarized to provide "lag time to 1st appointment" management reports.
- **Management Reports**: Periodic and cumulative summaries of key recruitment statistics that are provided at regular intervals or on an as needed basis. These reports help to inform recruitment and retention management decisions. Samples reports are provided in the Appendix section.

Optional Supplementary Programs

Direct Mail Campaign
Well-designed, strategically targeted direct mail campaigns are a proven means of encouraging consumer response. A direct mail campaign targeting individuals 50 and older already diagnosed with diabetes will reach approximately 123,000 people in and around the counties in which there are clinical trial sites. By targeting this selected demographic, we can more efficiently and cost effectively reach potential trial participants.

A compelling direct mail piece can anticipate and address the most commonly asked questions about the research being conducted and emphasizes the benefits of participating in the trial, as well as providing customized information on individual sites. In addition, the piece can provide the option of calling the study 800 number or responding directly to the study site via a reply card. If the latter option is chosen, the study coordinator will contact the patient directly for follow-up and further screening.

Benefits
- A targeted approach will save time and money in reaching the most promising candidates for the study
- Written materials provide an opportunity to reinforce key messages about the study
- Response to the mailing is measurable
- Immediate response facilitates accelerated screening and enrollment

Implementation Logistics
- Rent/buy appropriate lists of self-reported diabetics over 50-years-old
- Design and write a generic piece which will be customized to each market
- Provide a perforated reply card
- Facilitate central and local IRB review and approval
- Manage printing and mailing of the piece
- Evaluate success via ongoing communications with study sites and tracking calls to the 800-number generated by the direct mail piece

Physician Referral Expansion Pilot Program
GCI will provide and manage the services of a partner organization with expertise in generating physician referrals. We will identify five sites to participate in a pilot program and systematically review processes for encouraging referrals. Through interviews with investigators and coordinators and reviews of patient, medical center, clinic and hospital databases, we will identify physicians relevant to the study and determine areas for improvement in dealing with them. Based on the findings, we will develop and implement an action plan for accelerating and enhancing the enrollment process. Based on the level of success and timing, we may wish to expand this program to additional markets.

Benefits
- Physician referrals offer a targeted, efficient approach to identifying patients who meet very specific inclusion/exclusion criteria for study

Implementation Logistics
- Identify pilot sites, which would benefit most from a referral network

- Conduct and analyze site-by-site review of current "referral generating" practices and impact of "medical political" climate and dynamics.
- •Mine site's internal and external medical community for physicians relevant to the study referral (via databases for medical centers, hospitals and larger clinics)
- Collaborate with local investigator and study coordinator to identify viable referral sources.
- Implement market-specific physician referral generation program including
- face-to-face meetings with potential referring physicians, written materials and ongoing contact to keep study "top of mind."

Study Site and IRB Relations

GCI recommends an overall strategy of responsive partnership with the study sites. GCI will implement this strategy through direct interaction with site personnel on a regular basis, once the centralized program is launched. A site database will be created and maintained by Phone Screen and GCI.

Benefits

- Enhanced relationships with site coordinators and investigators may increase their interest/commitment to Abbott trials over those of competitors
- Additional support for site coordinators and investigators may serve as an incentive to take on more patients

Implementation Logistics

- Contact all study site investigators (in writing only) and coordinators (by telephone and in writing) to introduce the GCI Healthcare Site Relations Manager, the recruitment support program being planned by Abbott and GCI, and review program procedures and responsibilities for the site
- Assess site's experience with and receptivity to centralized recruitment programs, referral call back capabilities and obtain local recruitment suggestions from coordinator/investigator
- Maintain ongoing contact with site coordinator during program implementation to inform of advertising plans, assess progress, referral tracking, etc. Document important conversations on Site Relations Tracking Worksheet
- Submit radio script, call guide and FAQ documents to central IRBs and sites with local IRBs for review and approval
- Track receipt of IRB approvals; notify call center of approval and activate advertising in specific market
- Conduct periodic teleconference calls with sites to assess recruitment program progress, enrollment status, etc.
- Inform Abbott of "critical" site issues relevant to recruitment program that emerge
- Provide Abbott with copies of site correspondence for investigator files

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